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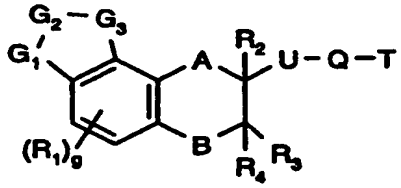
(57) Abstract



(I)

Compounds of formula (I) and pharmaceutically acceptable salts thereof in which A is methylene or –O–; B is methylene or –O–; G_1–G_2–G_3 form a heteroaromatic or heteroaliphatic chain; g is 0, 1 or 2; U is an alkylene chain optionally substituted by one or more alkyl; Q represents a divalent group containing nitrogen atoms; and T is an optionally substituted aryl or heteroaryl group, have utility in the treatment of central nervous system disorders, for example depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive–compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non–insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity.

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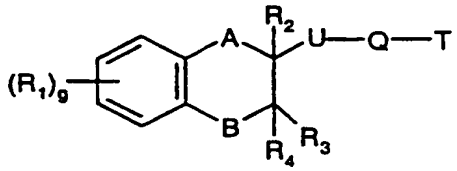
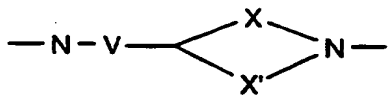
DIOXINO DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

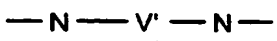
The present invention relates to novel dioxinoindole and thienobenzodioxin compounds which have affinity for 5-HT_{1A} and/or D_2-like (D_2, D_3 and/or D_4 sub-types) receptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of central nervous system disorders, for example depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity.

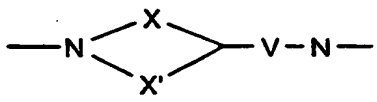
WO9507274 discloses compounds of the general formula



in which R_1 is selected from a number of substituents or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring, A and B are -O- or methylene, U is an alkylene chain, Q is selected from the following:

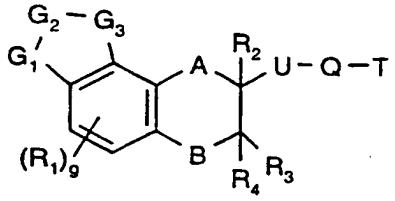






and T is an optionally substituted aromatic group optionally containing one or more N atoms. These compounds are described as being useful in the treatment of central nervous system disorders.

The present invention provides compounds of formula I



I

including pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers, in which

A is methylene or -O-;

B is methylene or -O-;

G_1-G_2-G_3 represent -N(R′)-C(R″)=N-, -N=C(R″)-N(R′)-, -N(R′)-C(R″)=C(R‴)-, -C(R‴)=C(R″)-N(R′)-, -N(R′)-N=C(R″)-, -C(R″)=N-N(R′)-, -N(R′)-N=N-, -N=N-N(R′)-, -N=C(R″)-O-, -N=C(R″)-S-, -O-C(R″)=N-, -S-C(R″)=N-, -O-N=C(R″)-, -S-N=C(R″)-, -C(R″)=N-O-, -C(R″)=N-S-, -S-C(R″)=C(R‴)-, -C(R″)=C(R‴)-S-, -O-C(R″)=C(R‴)-, -C(R″)=C(R‴)-O- or -O-C(R′)(R′)-O- wherein

R′ is H or an alkyl group containing 1 to 3 carbon atoms; and

R″ and R‴, which are the same or different, are H; halo; an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; carboxy; an alkanoyl group containing 1 to 6 carbon atoms; an alkoxycarbonyl group in which the alkoxy group contains 1 to 3 carbon atoms; formyl; cyano; or a carbamoyl group or carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups, which may be the same or different, each containing 1 to 3 carbon atoms;

g is 0, 1 or 2;

R_1 represents an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo; halo; or an alkylthio group containing 1 to 3 carbon

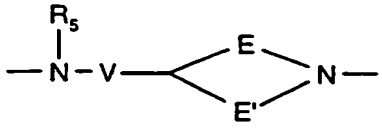
atoms optionally substituted by one or more halo; the substituents represented by R_1 being the same or different when g is 2;

R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

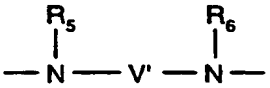
R_3 and R_4, which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

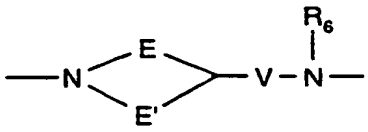
Q represents a divalent group of formula IIa, IIb or IIc



IIa



IIb



IIc

in which V is $(CH_2)_n$, wherein n is 0, 1, 2 or 3, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

V' is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

E is an alkylene chain containing 0 to 2 carbon atoms and E' is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in E and E' amounts to 3 or 4; and

R_5 and R_6, which may be the same or different, are H or an alkyl group containing 1 to 4 carbon atoms; and

T represents phenyl, 1- or 2-naphthyl, 1-naphth[2,1-*d*][1,2,3]oxadiazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 3- or 7-benzo[*b*]furanyl, 2,3-dihydro-7-benzo[*b*]furanyl, 2-, 3- or 7-benzo[*b*]thiophenyl, 3-, 4- or 5-pyrazolyl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-2-yl, 5-tetrazolyl, 2-, 3- or 4-quinolinyl, 2- or 4-quinazolinyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl or 2-, 4- or 5-thiazolyl each of which may be optionally substituted by one or more substituents selected from a) halo, b) an alkyl group containing 1 to 4 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 5 carbon atoms, n) 1-pyrrolidinyl or 1-piperidinyl, o) nitro or p) acetamido.

In preferred compounds of formula I, A is -O-.

In preferred compounds of formula I, B is -O-.

In more preferred compounds of formula I, both A and B are -O-.

In preferred compounds of formula I, g is 0 or 1. When g is 1, R_1 is preferably halo or an alkyl group containing 1 to 3 carbon atoms. In more preferred compounds of formula I, g is 0.

In preferred compounds of formula I, G_1-G_2-G_3 are -N(R′)-C(R″)=C(R‴)-; -S-C(R″)=C(R‴)-, -N(R′)-N=C(R″)-,. -O-C(R″)=C(R‴)-, or -O-C(R′)(R′)-O-.

Preferably, R′ is H, R″ is H or alkoxycarbonyl (more preferably H or ethoxycarbonyl), and R‴ is H or halo (more preferably H or chloro). In more preferred compounds of formula I, G_1-G_2-G_3 are -O-C(R″)=C(R‴)- and R″ and R‴ are both H.

In preferred compounds of formula I, R_2 is H.

In preferred compounds of formula I, R_3 and R_4, are both H.

In preferred compounds of formula I, U is methylene.

In preferred compounds of formula I, Q is a group of formula IIa in which V is methylene, E and E′ are both ethylene and R_5 is H.

In preferred compounds of formula I, T is phenyl or naphthyl, each of which may be optionally substituted by one or more substituents selected from an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or halo (more preferably the substituent is methoxy). In more preferred compounds of formula I, T is phenyl optionally substituted by one or more substituents selected from an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or halo (more preferably the substituent is methoxy). In especially preferred compounds of formula I, T is 2-methoxyphenyl or 2-hydroxyphenyl.

In one group of preferred compounds of formula I, both A and B are -O-; g is 0, G_1-G_2-G_3 are -NH-CH=CH-; -NH-C($CO_2C_2H_5$)=CH-; -S-CH=CH-; S-CH=C(Cl)-; -NH-N=CH-; -O-CH=CH-; or -O-CH_2-O-; R_2 is H; R_3 and R_4 are both H; U is methylene; Q is a group of formula IIa in which V is methylene, E and E′ are both ethylene and R_5 is H; and T is phenyl optionally substituted by hydroxy or by one or more alkoxy groups each containing 1 to 3 carbon atoms. More preferably, G_1-G_2-G_3 are -S-CH=CH- or -O-CH=CH-. Most preferably G_1-G_2-G_3 are -O-CH=CH-.

In another group of preferred compounds of formula I, both A and B are -O-; g is 0; G_1-G_2-G_3 are -N(R′)-C(R″)=C(R‴)- wherein R′ is H, R″ is H or alkoxycarbonyl in which the alkoxy group contains 1 to 3 carbon atoms, and R‴ is H or halo; R_2, R_3 and

R_4 are each H; U is methylene; Q is a group of formula IIa in which V is methylene, E and E′ are both ethylene and R_5 is H; and T is phenyl optionally substituted by hydroxy or one or more alkoxy groups.

In another group of preferred compounds of formula I, both A and B are -O-; g is 0; G_1-G_2-G_3 are -S-C(R″)=C(R‴)- wherein R ″ is H or alkoxycarbonyl in which the alkoxy group contains 1 to 3 carbon atoms, and R‴ is H or halo; R_2, R_3 and R_4 are each H; U is methylene; Q is a group of formula IIa in which V is methylene, E and E′ are both ethylene and R_5 is H; and T is phenyl optionally substituted by hydroxy or one or more alkoxy groups.

In another group of preferred compounds of formula I, both A and B are -O-; g is 0; G_1-G_2-G_3 are -O-C(R″)=C(R‴)- wherein R ″ is H or alkoxycarbonyl in which the alkoxy group contains 1 to 3 carbon atoms, and R‴ is H or halo; R_2, R_3 and R_4 are each H; U is methylene; Q is a group of formula IIa in which V is methylene, E and E′ are both ethylene and R_5 is H; and T is phenyl optionally substituted by hydroxy or one or more alkoxy groups.

In another group of preferred compounds of formula I, both A and B are -O-; g is 0; G_1-G_2-G_3 are -O-C(R′)(R′)-O- wherein R′ is H, R_2, R_3 and R_4 are each H; U is methylene; Q is a group of formula IIa in which V is methylene, E and E′ are both ethylene and R_5 is H; and T is phenyl optionally substituted by hydroxy or one or more alkoxy groups.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. The present invention includes all such salts. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

It will be understood that any group mentioned herein which contains a chain of three or more atoms signifies a group in which the chain may be straight or branched.

For example, an alkyl group may comprise propyl, which includes *n*-propyl and isopropyl, and butyl, which includes *n*-butyl, *sec*-butyl, isobutyl and *tert*-butyl. The term 'halo' as used herein signifies fluoro, chloro, bromo and iodo.

Compounds of formula I and intermediates in their preparation contain one or more chiral centres, and exist in different optically active forms. When compounds of formula I and intermediates in their preparation contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to this skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Specific compounds of formula I are:-

N-(9-Chloro-2,3-dihydrothieno[3,2-*f*][1,4]-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(2,3-Dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

Ethyl 2,3-dihydro-2-(*N*-{[1-(2-methoxyphenyl)piperid-4-yl]methyl}aminomethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate;

N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indazol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

2-{4-[(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)aminomethyl]piperidino}-phenol;

N-(7,8-Methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

Specific enantiomeric forms of compounds of formula I include:

(*S*)-*N*-(9-Chloro-2,3-dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(S)-N-(2,3-Dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl) piperid-4-yl]methylamine;

Ethyl (*S*)-2,3-dihydro-2-(*N*-{[1-(2-methoxyphenyl)piperid-4-yl]methyl}aminomethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate;

(*S*)-N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)-1-[1-(2-methoxyphenyl)-piperid-4-yl]methylamine;

(*S*)-N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indazol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine

(*S*)-*N*-(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine

(S)-2-{4-[(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)aminomethyl]-piperidino}phenol;

(*S*)-*N*-(7,8-Methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine

and pharmaceutically acceptable salts thereof.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt thereof together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term "active compound" denotes a compound of formula I or a salt thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if

desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethyl- cellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Pharmaceutical compositions may also be administered parenterally (for example subcutaneously, intramuscularly, intradermally and/or intravenously [such as by injection and/or infusion]) in the known pharmaceutical dosage forms for parenteral administration (for example sterile suspensions in aqueous and/or oily media and/or sterile solutions in suitable solvents, preferably isotonic with the blood of the intended patient). Parenteral dosage forms may be sterilised (for example by micro-filtration and/or using suitable sterilising agents [such as ethylene oxide]). Optionally one or more of the following pharmaceutically acceptable adjuvants suitable for parenteral administration may be added to parenteral dosage forms: local anaesthetics, preservatives, buffering agents and/or mixtures thereof. Parenteral dosage forms may be stored in suitable sterile sealed containers (for example ampoules and/or vials) until use. To enhance stability during storage the parenteral dosage form may be frozen after filling the container and fluid (for example water) may be removed under reduced pressure.

Pharmaceutical compositions may be administered nasally in known pharmaceutical forms for such administration (for example sprays, aerosols, nebulised solutions and/or powders). Metered dose systems known to those skilled in the art (for example aerosols and/or inhalers) may be used.

Pharmaceutical compositions may be administered to the buccal cavity (for example sub-lingually) in known pharmaceutical forms for such administration (for example slow dissolving tablets, chewing gums, troches, lozenges, pastilles, gels, pastes, mouthwashes, rinses and/or powders).

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, for example paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound

present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The present invention also comprises a compound of formula I for use as a medicament.

The compounds of formula I or salts thereof or pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt thereof may be used to treat depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity in human beings. Preferably, the compounds of formula I are used to treat psychoses, for example schizophrenia. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

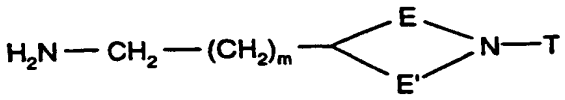
A further aspect of the present invention provides the use of a compound of formula I in the manufacture of a medicament for treating depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-

compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity in human beings. Preferably, there is provided a compound of formula I for use in the manufacture of a medicament for treating psychoses, for example schizophrenia.

The present invention also provides a method of treating depression, anxiety, psychoses (for example schizophrenia), tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity in human beings which comprises the administration of a therapeutically effective amount of a compound of formula I to a patient in need thereof. Preferably, the method is a method of treating psychoses, for example schizophrenia.

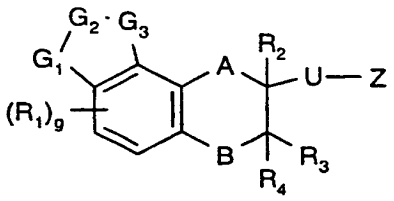
Processes for the preparation of compounds of formula I will now be described. These processes form a further aspect of the present invention. The processes are preferably carried out at atmospheric pressure, at a temperature in the range minus 80°C to 300°C more preferably in the range 0-200°C, and most preferably in the range 20-150°C. The substituents are as defined for formula I above unless otherwise stated.

Compounds of formula I in which Q is a group of formula IIa in which R_5 is H, and V is $(CH_2)_n$ wherein n is 1, 2 or 3 may be prepared by reaction of a compound of formula III



III

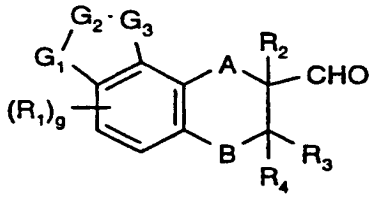
in which m is 0, 1 or 2, with a compound of formula IV



IV

in which Z is a leaving group, for example toluene-4-sulphonyloxy, optionally in the presence of a suitable solvent, for example acetonitrile, optionally in the presence of a base, for example potassium carbonate, and optionally in the presence of a catalyst, for example potassium iodide.

Compounds of formula I in which U is methylene and Q is a group of formula IIa in which R_5 is H, and V is $(CH_2)_n$ wherein n is 1, 2 or 3, and R″ and R‴ are other than formyl may be prepared by reaction of a compound of formula V

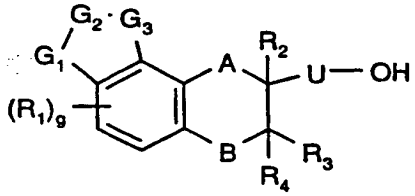


V

with a compound of formula III, followed by reduction of the intermediate imine with a suitable reducing agent, for example sodium borohydride.

Compounds of formula III and methods for their preparation are known (for example in WO95/07274).

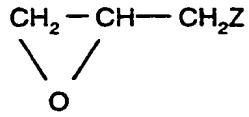
Compounds of formula IV in which Z is toluene-4-sulphonyloxy may be prepared by reaction of a compound of formula VI



VI

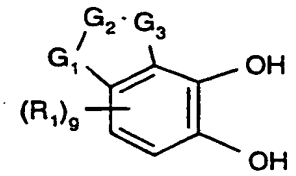
with toluene-4-sulphonyl chloride, optionally in the presence of a base, for example pyridine or 4-dimethylaminopyridine.

Compounds of formula VI in which A and B are both -O-, R_2, R_3 and R_4 are all H, and U is methylene may be prepared by reaction of a compound of formula VII



VII

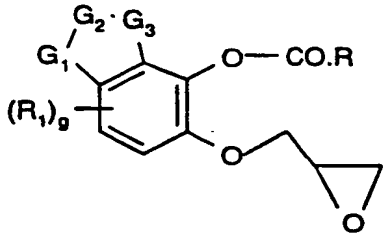
in which Z is a leaving group, for example chloro or toluene-4-sulphonyloxy, with a compound of formula VIII



VIII

in a suitable solvent, for example water or dimethylformamide in the presence of a base, for example sodium hydroxide. When the appropriate enantiomerically pure form of a compound of formula VII, for example (*R*)-glycidyl 4-toluenesulphonate, is used, the single (*S*)-enantiomer of a compound of formula VI can be prepared.

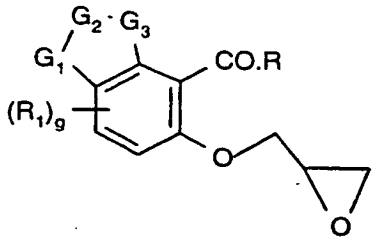
Compounds of formula VI in which A and B are both -O-, U is methylene, and R_2, R_3 and R_4 are all H, may also be prepared by cyclisation of a compound of formula IX



IX

in which R is H or an alkyl group containing 1 to 4 carbon atoms, using a base, for example potassium carbonate.

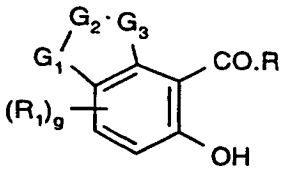
Compounds of formula IX may be prepared by oxidation of compounds of formula X



X

in which R is H or an alkyl group containing 1 to 4 carbon atoms, with a peroxyacid, for example 3-chloroperoxybenzoic acid.

Compounds of formula X may be prepared by alkylating compounds of formula XI



XI

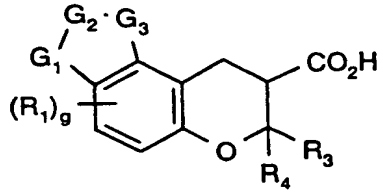
in which R is H or an alkyl group containing 1 to 4 carbon atoms, with compounds of formula VII, in which Z is a leaving group, for example chloro or toluene-4-sulphonyloxy, in a suitable solvent, for example dimethylformamide, in the presence of a base, for example potassium carbonate. When the appropriate enantiomerically pure form of a compound of formula VII, for example (*R*)-glycidyl 4-toluenesulphonate, is used, the single (*S*)-enantiomer of a compound of formula VI can be prepared.

Compounds of formula VI in which A and B are both -O-, U is methylene, R_2, R_3 and R_4 are all H, and the group $-G_1-G_2-G_3-$ contains the group R″ which is as stated below, may be prepared as follows:

- when R″ is H or CO_2Et, the compound of formula VI may be prepared by cyclisation of the appropriate compound of formula IX in the presence of potassium carbonate;
- when R″ is CO_2H, the compound of formula VI may be prepared by hydrolysis of the corresponding compound of formula VI in which R″ is CO_2Et;
- when R″ is H, the compound of formula VI may also be prepared by decarboxylation of the corresponding compound of formula VI in which R″ is CO_2H;

- when R″ is $CONH_2$, the compound of formula VI may be prepared by reaction of the corresponding compound of formula VI in which R″ is CO_2Et, CO_2H, CO.Cl or $CO.O.CO_2Et$ with ammonia, in the presence, where appropriate, of an amide coupling agent such as carbonyl diimidazole;
- when R″ is $CONMe_2$, the compound of formula VI may be prepared by reaction of the corresponding compound of formula VI in which R″ is CO_2Et, CO_2H, CO.Cl or $CO.O.CO_2Et$ with dimethylamine, in the presence, where appropriate, of an amide coupling agent such as carbonyl diimidazole;
- when R″ is CHO, the compound of formula VI may be prepared by reduction of the corresponding compound of formula VI in which R″ is CO_2Et;
- when R″ is COMe, the compound of formula VI may be prepared by reaction of the corresponding compound of formula VI in which R″ is CO_2H with methyl lithium; and
- when R″ is CN, the compound of formula VI may be prepared by dehydration of the corresponding compound of formula VI in which R″ is $CONH_2$.

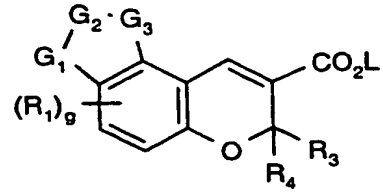
Compounds of formula VI in which A and U are methylene, B is -O-, R_2 is H and R″ and R‴ are H or cyano, may be prepared by reduction of a compound of formula XII



XII

with a reducing agent, for example borane-dimethyl sulphide complex.

Compounds of formula XII may be prepared by reduction of a compound of formula XIII

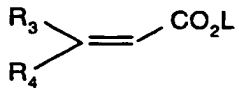


XIII

in which L is H with a reducing agent, for example hydrogen in the presence of a palladium-on-carbon catalyst.

Compounds of formula XIII in which L is H may be prepared by acid or base-catalysed hydrolysis of a compound of formula XIII in which L is an alkyl group containing 1 to 6 carbon atoms.

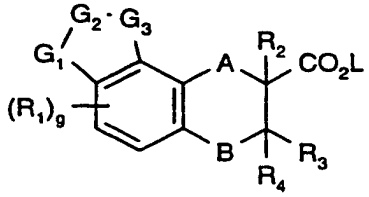
Compounds of formula XIII in which L is an alkyl group may be prepared by reaction of a compound of formula XI in which R is H with a compound of formula XIV



XIV

in which L is an alkyl group containing 1 to 6 carbon atoms, in the presence of a base, for example 1,4-diazabicyclo[2.2.2]octane (DABCO).

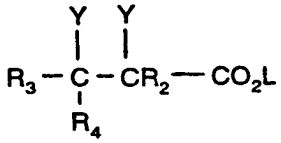
Compounds of formula V may be prepared by oxidation of a compound of formula VI in which U is methylene with a suitable oxidising agent, for example pyridinium chlorochromate or by reduction of a compound of formula XV



XV

with a suitable reducing agent, for example sodium bis(2-methoxyethoxy)aluminium hydride in a solvent, for example toluene.

Compounds of formula XV in which A and B are both -O- may be prepared by reaction of a compound of formula XVI

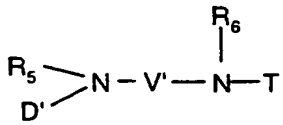


XVI

in which Y is a leaving group, for example bromo, and L is an alkyl group containing 1 to 6 carbon atoms with a compound of formula VIII, in the presence of a base, for example potassium carbonate.

Compounds of formula XV in which A is methylene, B is -O-, R_2 is H and L is an alkyl group containing 1 to 6 carbon atoms may be prepared by reduction of a compound of formula XIII in which L is an alkyl group containing 1 to 6 carbon atoms, with a suitable reducing agent, for example hydrogen in the presence of a palladium-on-carbon catalyst.

Compounds of formula I in which Q is a group of formula IIb may be prepared by reaction of a compound of formula IV in which Z is a leaving group, for example toluene-4-sulphonyloxy, with a compound of formula XVII

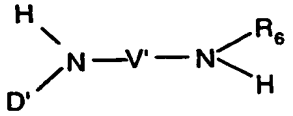


XVII

in which D′ is H, optionally in the presence of a base, for example potassium carbonate, and optionally in a solvent, for example acetonitrile.

Compounds of formula XVII in which D′ is H may be prepared by deprotection of a compound of formula XVII in which D′ is a protecting group, for example *tert*-butoxycarbonyl, for example by hydrolysis in the presence of an acid, for example trifluoroacetic acid.

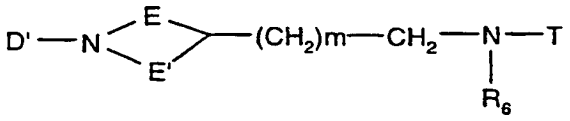
Compounds of formula XVII in which D′ is a protecting group may be prepared by reaction of a compound of formula XVIII



XVIII

in which D′ is a protecting group, for example *tert*-butoxycarbonyl, with a haloaromatic compound, for example a 2-halopyridine such as 2-chloropyridine, optionally in the presence of a base, for example triethylamine, in a suitable solvent such as dichloromethane.

Compounds of formula I in which Q is a group of formula IIc in which V is $(CH_2)_n$ wherein n is 1, 2, or 3 may be prepared by reaction of a compound of formula XIX

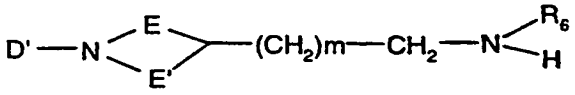


XIX

in which D′ is H and m is 0, 1 or 2, with a compound of formula IV in which Z is a leaving group, for example toluene-4-sulphonyloxy, optionally in the presence of a base, for example potassium carbonate, and optionally in a solvent, for example acetonitrile.

Compounds of formula XIX in which D′ is H may be prepared by deprotection of a compound of formula XIX in which D′ is a protecting group, for example *tert*-butoxycarbonyl, for example by hydrolysis in the presence of an acid, for example trifluoroacetic acid.

Compounds of formula XIX in which D′ is a protecting group may be prepared by reaction of a compound of formula XX



XX

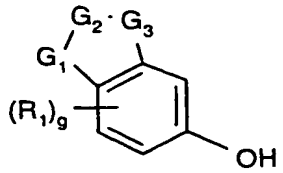
in which D′ is a protecting group, for example *tert*-butoxycarbonyl, and m is 0, 1 or 2, with a haloaromatic compound, for example a 2-halopyridine such as 2-chloropyridine, optionally in the presence of a base, for example triethylamine, in a suitable solvent such as dichloromethane.

Compounds of formula IV in which G_1-G_2-G_3 are -NH-CH=CH- are known (J.Med.Chem.,1992,35, pg 3058).

Compounds of formula IV in which G_1-G_2-G_3 are other than -NH-CH=CH- may be prepared by methods analogous to that described above.

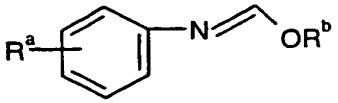
Compounds of formula I in which R_5 is an alkyl group and R″ and R‴ are other than formyl may be prepared by alkylation of a compound of formula I in which R_5 is H with for example formaldehyde and formic acid, or an aldehyde and a reducing agent such as sodium cyanoborohydride.

Compounds of formula XI in which R is H may be prepared by reaction of a compound of formula XXI



XXI

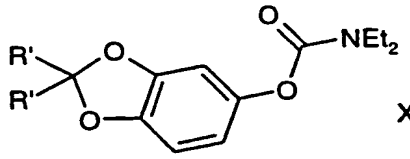
with an *N*-arylformimidate ester of formula XXII



XXII

in which R^a is H, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or halo, and R^b is an alkyl group containing 1 to 3 carbon atoms, for example ethyl *N*-(4-methoxyphenyl)formimidate, followed by hydrolysis of the intermediate imine in the presence of an acid.

Compounds of formula XI in which R = H and G1-G2-G3 represents -O-$C(R')_2$-O- may be prepared by reaction of a compound of formula XXIII



XXIII

with a lithiating agent, for example sec-butyllithium, followed by a formylating agent, for example N,N-dimethylformamide, followed by hydrolytic work-up.

Compounds of formula XXIII may be prepared by reaction of compounds of formula XXI with diethylcarbamoyl chloride in the presence of a base, for example sodium hydride.

Compounds of formula I in which the group T bears a hydroxy substituent may be prepared by dealkylation of a corresponding alkoxy substituted compound, by reaction with a dealkylating agent, for example pyridine hydrochloride.

Compounds of formula I in which G1-G2-G3 represents -S-CH=CH- may be prepared by dechlorination of a corresponding compound in which G1-G2-G3 represents -S-CH=CCl- by, for example, reaction with hydroiodic acid.

The ability of compounds of formula I to interact with 5-hydroxytryptamine (5-HT) receptors has been demonstrated by the following test which determines the ability of the compounds to inhibit tritiated ligand binding to 5-HT receptors in vitro and in particular to 5-HT_{1A} receptors.

Hippocampal tissue from the brains of male Charles River CD rats weighing between 150-250 g were homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7) when measured at 25°C, 1:40 w/v) and centrifuged at 30,000 g at 4°C for 10 minutes. The pellet was rehomogenised in the same buffer, incubated at 37°C for 10 minutes and centrifuged at 30,000 g at 4°C for 10 minutes. The final pellet was resuspended in 50 mM Tris-HCl buffer (pH 7.7) containing 4 mM $CaCl_2$, 0.1% L-ascorbic acid and 10 µM pargyline hydrochloride (equivalent to 6.25 mg wet weight of tissue/ml) and used immediately in the binding assay. Aliquots (400 µl; equivalent to 2.5 mg wet weight of tissue/tube) of this suspension were added to tubes containing the ligand (50 µl; 2 nM) and distilled water (50 µl; total binding) or 5-HT (50 µl; 10 µM; non-specific binding) or test compound (50 µl; at a single concentration of 10^{-6} M or at 10 concentrations ranging from 10^{-11}-10^{-3} M). The ligand was [^{3}H]8-hydroxy-2-(dipropylamino)tetralin ([^{3}H]8-OH-DPAT) and the mixture was incubated at 25°C for 30 minutes before the incubation was terminated by rapid filtration.

The filters were washed with ice-cold Tris-HCl buffer and dried. The filters were punched out into vials, scintillation fluid added and radioactivity determined by liquid scintillation counting. The percentage displacement of specific binding of the tritiated ligand was calculated for the single concentration (10^{-6} M) of test compound. Displacement curves were then produced for those compounds which displaced ≥50% of specific binding of the tritiated ligand at 10^{-6} M using a range of concentrations of the compound. The concentration which gave 50% inhibition of specific binding (IC_{50}) was obtained from the curve. The inhibition coefficient Ki was then calculated using the formula

$$K_i = \frac{IC50}{1+([ligand]/K_D)}$$

in which [ligand] is the concentration of the tritiated ligand used and K_D is the equilibrium dissociation constant for the ligand.

The ability of compounds of formula I to interact with dopamine receptors has been demonstrated by the following test which determines the ability of the compounds to inhibit tritiated ligand binding to dopamine receptors in vitro and in particular to the D_2-like dopamine receptors.

Striatal tissue from the brains of male Charles River CD rats weighing between 140-250g were homogenised in ice-cold 50 mM Tris-HCl buffer (pH 7.7 when measured at 25°C) and centrifuged at 40,000 g for 10 minutes. The pellet was resuspended in Tris salts buffer (50 mM Tris-HCl buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 1 mM $MgCl_2$ with the addition of 6 mM ascorbic acid; pH 7.7 when measured at 25°C), and again centrifuged at 40,000 g for 10 minutes. The final pellet was stored at -80°C. Before each test the pellet was resuspended in Tris salts buffer (equivalent to 2 mg wet weight of tissue/ml). Aliquots (720 µl; equivalent to 1.44 mg wet weight of tissue/tube) of this suspension were then added to tubes containing the ligand (40 µl; 1 nM) and Tris salts buffer (40 µl; total binding) or spiroperidol (40 µl; 10 nM; non-specific binding) or test compound (40 µl; at a single concentration of 10^{-6}M or at 6 concentrations ranging from 10^{-11}-10^{-4}M). The ligand was tritiated (*S*)-sulpiride and the mixture was incubated at 4°C for 40 minutes before the incubation was terminated by rapid filtration.

The filters were washed with ice-cold Tris-HCl buffer and dried. The filters were punched out in to vials, scintillation fluid added and were left for about 20 hours before being counted by scintillation spectrophotometry. The percentage displacement of specific binding of the tritiated ligand was calculated for the single concentration (10^{-6}M) of test compound. Displacement curves were then produced over a range of concentrations for those compounds which displaced ≥50% of specific binding of the tritiated ligand at 10^{-6}M. The concentration which gave a 50% inhibition

of specific binding (IC50) was obtained from the curve. The inhibition coefficient Ki was then calculated using the formula

$$K_i = \frac{IC50}{1+([ligand]/K_D)}$$

in which [ligand] is the concentration of the tritiated ligand used and K_D is the equilibrium dissociation constant for the ligand.

The K_i values obtained in the above tests for 5-HT_{1A} and D_2-like binding for each of the final products of the Examples hereinafter are given in Table I below.

TABLE 1

Example Number	Ki (nM) value for	
	5-HT_{1A}	D_2-like
1	36	76.9
2	9.7	40.4
3	99%	106
4	99%	8.96
5	1.2	7.1
6	1.7	22.1
7	3.6	11.7
8	1.1	6

The % figures in Table 1 are for % displacement at 10^{-6}M.

Advantageous compounds of the present invention have a Ki of less than 100nM for 5-HT_{1A} or a binding affinity for 5-HT_{1A} of greater than 90% at 10^{-6}M and a Ki of less than 100nM for D_2-like receptors or a binding affinity for D_2-like receptors of greater than 90% at 10^{-6}M.

The invention is illustrated by the following Examples which are given by way of example only. The final product of each Example was characterised by one or more of

the following procedures: gas-liquid chromatography; high performance liquid chromatography; elemental analysis, nuclear magnetic resonance spectroscopy, infrared spectroscopy and spectroscopy.

Example 1

A stirred solution of ethyl 3-chloro-5-methoxybenzo[*b*]thiophene-2-carboxylate (20.0 g) in dichloromethane (80 ml) at -20°C under an atmosphere of nitrogen was treated with boron tribromide (1M solution in dichloromethane; 90 ml) and the solution allowed to warm up to room temperature slowly. After 2 hours the mixture was carefully poured into ethanol (400 ml) and left to stand for 10 minutes. The solvent was evaporated under reduced pressure and the residue dissolved in ethyl acetate (500 ml). The resulting solution was washed with water (300 ml), dried over sodium sulphate and the solvent evaporated under reduced pressure to give ethyl 3-chloro-5-hydroxybenzo[*b*]thiophene-2-carboxylate (18.68 g) as an off-white solid; m.p. 160-161°C.

A round bottomed flask containing a mixture of the product from the previous reaction (6.04 g) and ethyl *N*-(4-methoxyphenyl)formimidate (4.50 g) was submerged rapidly in an oil bath pre-heated to 160°C, and the mixture stirred at 160-80°C for 4 hours, the ethanol produced in the reaction being removed by distillation. More of the formimidate (0.80 g) was then added and the mixture heated at 180-90°C for a further 1 hour. The cooled mixture was then treated with boiling methanol (100 ml) and the resulting light brown solid collected by filtration, washed with methanol (100 ml) and dried to give ethyl 3-chloro-5-hydroxy-4-[*N*-(4-methoxyphenyl)iminomethyl]benzo[*b*]thiophene-2-carboxylate (4.03 g); m.p. 162-163°C.

A stirred mixture of the product from the previous reaction (3.82 g) and hydrochloric acid (4M; 130 ml) was heated at 50-60°C for 4 hours and then left to stand at room temperature overnight. The mixture was then heated at 60-70°C for 3 hours. The cooled mixture was poured into water (350 ml) and extracted with ethyl acetate (2x250 ml). The combined organic extracts were washed with water (200

ml), dried over sodium sulphate and evaporated under reduced pressure to give ethyl 3-chloro-4-formyl-5-hydroxybenzo[*b*]thiophene-2-carboxylate (2.80 g) as a pale-green solid; m.p. 128-130°C.

Potassium carbonate (2.62 g) was added to a stirred solution of ethyl 3-chloro-4-formyl-5-hydroxybenzo[*b*]thiophene-2-carboxylate (4.90 g, prepared as described above) in dry dimethylformamide (50 ml) and then a solution of (*R*)-glycidyl tosylate (4.12 g) in dry dimethyl formamide (50 ml) was added slowly. The mixture was then stirred at 60°C for 3 hours, cooled and poured into water (1200 ml). The resulting pale-green solid was collected by filtration, washed with water (200 ml) and dried to give ethyl (*R*)-3-chloro-5-(2,3-epoxypropoxy)-4-formylbenzo[*b*]thiophene-2-carboxylate (5.15 g).

A stirred solution of the product from the previous reaction (1.0 g) in dichloromethane (20 ml) was treated with 3-chloroperoxybenzoic acid (85%; 0.75 g) and the mixture cooled to 0°C. A solution of trifluoroacetic acid (0.335 g) in dichloromethane (5 ml) was then added and the solution stirred at 0°C for 5 minutes and then at room temperature for 1 hour. The mixture was poured into saturated aqueous sodium bisulphite solution (100 ml) and extracted with dichloromethane (2x100 ml) . The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (2x150 ml), dried over sodium sulphate and evaporated under reduced pressure to give a brown oil. Purification by flash chromatography on silica using a 1:1 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate as eluant gave ethyl (*R*)-3-chloro-5-(2,3-epoxypropoxy)-4-formyloxybenzo[*b*]thiophene-2-carboxylate (0.52 g) as a pale-yellow solid.

Saturated aqueous potassium carbonate solution (20 ml) was added to a stirred solution of ethyl (*R*)-3-chloro-5-(2,3-epoxypropoxy)-4-formyloxy-benzo[*b*]thiophene-2-carboxylate (1.85 g, prepared as described above) in tetrahydrofuran (20 ml) and the mixture stirred for 24 hours at room temperature. The reaction mixture was poured into water (200 ml) and extracted with ethyl acetate (2x100 ml). The combined extracts were dried over sodium sulphate and evaporated under reduced pressure to give a yellow solid. Purification by flash chromatography on silica using a 1:1 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate as

eluant gave ethyl (*S*)-9-chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-*f*]-1,4-benzodioxin-8-carboxylate (1.44 g) as a pale-yellow solid; m.p. 165-166°C.

A stirred solution of the product from the previous reaction (1.30 g) in methanol (20 ml) was treated with a solution of lithium hydroxide monohydrate (0.17 g) in water (10 ml) and the mixture heated at 60°C for 1hour. The solution was evaporated under reduced pressure to remove methanol and then diluted with water (50 ml). The aqueous solution was acidified with hydrochloric acid (2 M) and the resulting suspension collected by filtration, washed with water and dried to give (*S*)-9-chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-*f*]-1,4-benzodioxin-8-carboxylic acid (1.15 g) as an off-white solid, m.p. 236-7°C.

A round bottomed flask containing a mixture of the product from the previous reaction (0.80 g) , copper powder (0.17 g) and quinoline (10 ml) was rapidly submerged in an oil bath pre-heated to 190°C, and the mixture heated with stirring at this temperature for 30 minutes. The mixture was cooled to room temperature and poured into hydrochloric acid (2M; 300 ml). The mixture was extracted with ethyl acetate (2x150 ml) and the combined extracts washed with hydrochloric acid (2M; 150 ml) , water (150 ml), then dried over sodium sulphate and evaporated under reduced pressure to give a dark brown oil (0.781 g). Purification by flash chromatography on silica using a 3:10 mixture of ethyl acetate and petroleum ether (b.p. 60-80°C) as eluant gave (*S*)-9-chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-*f*]-1,4-benzodioxin (0.70 g) as a white solid, m.p. 92-3°C.

4-Dimethylaminopyridine (0.26 g) then 4-toluenesulphonyl chloride (0.40 g) were added to a stirred solution of (*S*)-9-chloro-2,3-dihydro-2-(hydroxymethyl)thieno[3,2-*f*][1,4]-benzodioxin (0.49 g) in dichloromethane (20 ml), and the mixture then stirred at ambient temperature for 24 hours. The resulting solution was poured into water (100 ml) and extracted with dichloromethane (150 ml). The resulting organic solution was then washed successively with saturated copper sulphate solution (2 x 100 ml) and water (100 ml). The solution was dried over sodium sulphate and the solvent evaporated under reduced pressure to give (*S*)-9-chloro-2,3-dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl 4-toluene-sulphonate (0.7 g) as a white solid m.p. 169-70°C

A stirred mixture of the product from the previous reaction (0.63 g), potassium carbonate (3.0 g) and 1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (0.40 g) in dry acetonitrile (25 ml) was heated under reflux for 24 hours. The mixture was cooled, filtered and then evaporated under reduced pressure.The residue was dissolved in dichloromethane (150 ml), washed with water (100 ml), dried over sodium sulphate and the solvent evaporated under reduced pressure to give a pale-yellow oil (1.08 g). Purification by flash column chromatography on silica eluting with a 20:1 mixture of dichloromethane and methanol gave a colourless oil (0.47 g). The oil was dissolved in warm ethanol (2 ml) and a solution of fumaric acid (122 mg) in warm ethanol (2 ml) then added. The resulting white solid was collected by filtration and dried to give (*S*)-*N*-(9-chloro-2,3-dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine 0.5 fumarate (0.40 g) m.p. 171-172°C, $[\alpha]_D$ -30.4° (c = 0.237, MeOH).

Example 2

A stirred mixture of (*S*)-(-)-*N*-(9-chloro-2,3-dihydrothieno[3,2-*f*][1,4]-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine, prepared by the method described above (2.64 g) and hydroiodic acid (57%; 100 ml) was heated at 60-70°C for 6 hours and then allowed to stand at room temperature for 18 hours. The mixture was poured into aqueous ammonia (250 ml) and extracted with ethyl acetate (3 x 150 ml). The combined extracts were then washed with brine (200 ml), dried over sodium sulphate and the solvent evaporated under reduced pressure to leave a brown oil (2.72 g). Purification by flash column chromatography on silica eluting with a 95:5 mixture of dichloromethane and methanol, followed by repeat chromatography eluting with a 98:2 mixture of dichloromethane and methanol, gave a colourless oil (0.65 g). Fumaric acid (0.178 g) in ethanol (10 ml) was then added to a solution of the oil in ethanol (5 ml) and the solvent then removed under reduced pressure to give (*S*)-*N*-(2,3-dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine monofumarate (0.78 g) as an off-white solid; m.p. 180-182°C, $[\alpha]_D$ -28.1° (c=0.498, DMSO)

Example 3

Potassium carbonate (0.89 g) was added under nitrogen to a stirred solution of ethyl 4-formyl-5-hydroxyindole-2-carboxylate (1.50 g) in dry dimethylformamide (40 ml). A solution of (*R*)-glycidyl 4-toluenesulphonate (1.47 g) in dry dimethylformamide (30 ml) was then added and the mixture stirred at ambient temperature for 10 minutes, then at 60°C for 3 hours. The mixture was poured into water (400 ml) and extracted with ethyl acetate (3x200 ml). The combined extracts were washed with brine (6x200 ml), dried over magnesium sulphate and the solvent evaporated under reduced pressure. The brown solid residue was purified by flash column chromatography on silica eluting with a 1:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate to give ethyl (*R*)-5-(2,3-epoxypropoxy)-4-formylindole-2-carboxylate (1.07 g) as an off-white solid; m.p. 152-154 °C.

A stirred solution of ethyl (*R*)-5-(2,3-epoxypropoxy)-4-formylindole-2-carboxylate (1.95 g; prepared by the method described above) in dichloromethane (40 ml) was cooled to 0°C. 3-Chloroperoxybenzoic acid (85%; 1.75 g) was then added in one portion followed by a solution of trifluoroacetic acid (0.77g) in dichloromethane (10 ml), in portions. The mixture was stirred at 0°C for 10 minutes and then at ambient temperature for 1 hour. The reaction mixture was diluted with dichloromethane (300 ml) , washed successively with saturated aqueous sodium bisulphite solution (100 ml), saturated aqueous sodium bicarbonate solution (3x150 ml), dried over sodium sulphate and the solvent evaporated. The solid residue was purified by flash chromatography on silica eluting with a 1:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate to give ethyl (*R*)-5-(2,3-epoxypropoxy)-4-formyloxyindole-2-carboxylate (1.55 g) as a pale yellow crystalline solid; m.p. 123-125°C.

Saturated aqueous potassium carbonate solution (200 ml) was added to a stirred solution of ethyl (*R*)-5-(2,3-epoxypropoxy)-4-formyloxyindole-2-carboxylate (22.0 g; prepared in a similar manner to that described above) in tetrahydrofuran (250 ml) and the mixture was stirred at room temperature for 72 hours. The mixture was poured into water (1000 ml) and extracted with ethyl acetate (4x400 ml). The combined extracts were dried over sodium sulphate and the solvent evaporated

under reduced pressure to give ethyl (*S*)-2,3-dihydro-2-(hydroxymethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate (17.65 g) as a pale purple solid; m.p. 152-153°C.

4-Toluenesulphonyl chloride (2.23 g) was added in one portion to a stirred solution of ethyl (*S*)-2,3-dihydro-2-(hydroxymethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate (2.65 g) in dry dichloromethane (120 ml) at 0°C. 4-Dimethylaminopyridine (1.52 g) was then added and the cooling bath removed. The resulting solution was stirred at ambient temperature for 72 hours, then diluted with dichloromethane (150 ml) and washed successively with water (80 ml), saturated aqueous copper sulphate solution (2x100 ml), and then dried over sodium sulphate. Evaporation of the solvent under reduced pressure gave a purple foam which was purified by flash column chromatography on silica eluting with a 1:1 mixture of petroleum ether (b.p. 40-60 °C) and ethyl acetate, to give ethyl (*S*)-2,3-dihydro-2-[(4-toluenesulphonyloxy)methyl]-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate (3.71 g) as a colourless oil which solidified on standing.

A mixture of the product from the previous reaction (1.0 g), potassium carbonate (3.0 g) and 1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (0.80 g) in dry acetonitrile (50 ml) was heated under reflux with stirring for 24 hours. The cooled mixture was filtered and then evaporated under reduced pressure to give a yellow oil. The crude material was dissolved in dichloromethane (200 ml), washed with water (150 ml), dried over sodium sulphate and evaporated under reduced pressure to give a yellow oil (1.65 g). Purification by flash column chromatography on silica eluting with a 20:1 mixture of dichloromethane and methanol gave ethyl (*S*)-2,3-dihydro-2-(*N*-{[1-(2-methoxyphenyl)piperid-4-yl]methyl}aminomethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate 0.05 dichloromethane solvate (0.34 g) as an off-white solid m.p. 105-107°C, $[\alpha]_D$ -24° (c = 0.409, MeOH).

Example 4

A solution of lithium hydroxide monohydrate (0.94 g) in water (25 ml) was added to a stirred solution of the product from the previous reaction (2.95 g) in methanol (50 ml) under nitrogen and the resulting solution stirred at 60°C for 1 hour. The methanol was then removed by evaporation and water (80 ml) added. Hydrochloric acid (2M) was then added until the mixture was pH 2, and the resulting

precipitate collected by filtration, washed with water and dried to give (*S*)-2,3-dihydro-2-(hydroxymethyl)-7*H*-1,4-dioxino[2,3-e]indole-8-carboxylic acid (2.61g) as a solid; m.p. 216-217°C.

A flask containing the product from the previous reaction (2.60 g) was plunged into a pre-heated isomantle at 250°C under nitrogen and the material heated at 250-60°C for 30 minutes. The residue was cooled to ambient temperature, pre-absorbed from a methanol solution onto silica and purified by flash column chromatograhy on silica eluting with 1:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate to give (*S*)-2,3-dihydro-7*H*-1,4-dioxino-[2,3-*e*]indol-2-ylmethanol (0.69 g) as a colourless syrup.

A solution of (*S*)-2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethanol (0.75 g; prepared by the method described above) in dichloromethane (50 ml) was stirred with cooling in an ice bath. 4-(Dimethylamino)pyridine (0.59 g) and 4-toluenesulphonyl chloride (0.84 g) were then added and the solution stirred at ambient temperature overnight. The mixture was diluted with dichloromethane (200 ml) , washed sucessively with water (50 ml), saturated aqueous copper(II) sulphate solution (2x50 ml) and water (50 ml), then dried over sodium sulphate and the solvent evaporated to give (*S*)-2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl 4-toluenesulphonate (1.04 g) as a pale brown oil which solidified on standing.

A mixture of (*S*)-2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl 4-toluenesulphonate (2.76 g; prepared in a similar manner to that described above), potassium carbonate (8.0 g) and 1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (1.86 g) in dry acetonitrile (60 ml) was heated under reflux with stirring for 24 hours. The cooled mixture was filtered, the solid washed with dichloromethane (100 ml) and the filtrate then evaporated under reduced pressure . The residue was dissolved in dichloromethane (250 ml) and the resulting solution washed with water (100 ml), dried over sodium sulphate and evaporated under reduced pressure to give a fawn solid (4.51 g). Purification by flash column chromatography on silica eluting with a 20:1 mixture of dichloromethane and methanol gave (*S*)-*N*-(2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine 0.1

hydrate (1.34 g) as an off-white crystalline solid m.p. 162-163°C, $[\alpha]_D$ -18.5° (c= 0.541, CH_2Cl_2).

Example 5

A round bottomed flask containing a mixture of 5-hydroxy-1*H*-indazole (28.5 g) and ethyl *N*-phenylformimidate (35 g) was submerged rapidly in an oil bath pre-heated to 175°C and the mixture stirred at 160-180°C for 30 minutes, the ethanol produced in the reaction being removed by distillation. The cooled mixture was then treated with boiling methanol (500 ml) and the resultant brown solid collected by filtration, washed with methanol (100 ml) and dried to give 5-hydroxy-4-(*N*-phenyliminomethyl)-1*H*-indazole (32 g) as a yellow solid. The solid was dissolved in hydrochloric acid (5 M; 500 ml) and heated at 50-60°C with stirring for 2 hours. The mixture was diluted with water (500 ml) and extracted with ethyl acetate (2 x 500 ml). The combined extracts were washed with water (500 ml), dried over magnesium sulphate and the solvent evaporated under reduced pressure to give 5-hydroxy-1*H*-indazole-4-carboxaldehyde (15.48 g) as a yellow solid.

A mixture of potassium carbonate (11 g), the product from the previous reaction (12.5 g) and (*R*)-glycidyl tosylate (20 g) in dimethylformamide (250 ml) was stirred and heated at 50°C under an atmosphere of nitrogen for 3 hours. The mixture was poured into water (1000 ml) and extracted with ethyl acetate (3 x 300 ml). The combined extracts were washed with water (2 x 300 ml), dried over magnesium sulphate and the solvent evaporated under reduced pressure. The yellow solid residue was then purified by flash column chromatography on silica eluting with a 1:1 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate to give (*R*)-5-(2,3-epoxypropoxy)-1*H*-indazole-4-carboxaldehyde (2.58 g) as a pale yellow solid.

A solution of the product from the previous reaction (2.58 g) and 3-chloroperoxybenzoic acid (56-87%; 12.2 g) in dichloromethane (300 ml) was stirred at 0°C for 2 hours. The mixture was then evaporated to dryness and the residue dissolved in sodium hydroxide solution (2.5 M ; 200 ml). The navy blue solution was then heated on the steam bath for 1 hour with a resultant colour change to deep

orange. The cooled reaction mixture was diluted with water (200 ml) and extracted with ethyl acetate (3 x 250 ml). The combined extracts were washed with brine (250 ml), dried over magnesium sulphate and the solvent evaporated under reduced pressure to afford (*S*)-2-hydroxymethyl-7*H*-1,4-dioxino[2,3-*e*]indazole (0.97 g) as a cream solid.

A solution of 4-toluenesulphonyl chloride (2 g) in dichloromethane (100 ml) was added dropwise to a stirred solution the product from the previous reaction (0.95 g) and 4-dimethylaminopyridine (1.2 g) in dichloromethane (100 ml) at 0-5°C. The mixture was allowed to warm to room temperature and stirred for 18 hours. The solution was diluted with dichloromethane (30 ml) and washed successively with water (100 ml), dilute aqueous sodium hydrogen carbonate solution (5M; 2 x 100 ml), brine (2 x 100 ml) and then dried over magnesium sulphate. Evaporation of the solvent under reduced pressure gave a white solid residue which was then purified by flash column chromatography on silica using a 99:1 mixture of dichloromethane and ethyl acetate as eluant. The (*S*)-7-(4-toluenesulphonyl)-2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indazol-2-ylmethyl 4-toluenesulphonate produced which was dissolved in a mixture of 48% hydrobromic acid (2 ml) and phenol (0.4 g) and heated under reflux for 30 minutes. The cooled mixture was basified with sodium hydroxide (5M) and extracted with dichloromethane (3 x 25 ml). The combined extracts were washed with water (25 ml), dried over magnesium sulphate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica eluting with a 10:1 mixture of petroleum ether (b.p. 60-80°C) and ethyl acetate to give (*S*)-2,3-dihydro-7*H*-1,4-dioxino[2,3-*e*]indazol-2-ylmethyl 4-toluenesulphonate (0.53 g) as a white solid.

A mixture of the product from the previous reaction (0.25 g), potassium carbonate (2 g) and 1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (0.3 g) in a mixture of dimethylformamide (5 ml) and toluene (10 ml) was heated at reflux temperature for 8 hours. The cooled mixture was poured into water (100 ml) and extracted with ethyl ether (2 x 100 ml). The combined extracts were then dried over magnesium sulphate and the solvent removed under reduced pressure to yield a yellow oil. Purification by flash column chromatography on silica eluting with a 20:1 mixture of dichloromethane and methanol afforded (*S*)-*N*-(2,3-dihydro-7*H*-1,4-

dioxino[2,3-*e*]indazol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (0.04 g) as a gummy solid.

Example 6

Potassium carbonate (2.85 g) and a solution of (*R*)-glycidyl 4-toluensulphonate (4.50 g) in dry dimethylformamide (10 ml) were added to a stirred solution of 5-hydroxybenzo[*b*]furan-4-carboxaldehyde (3.04 g) in dry dimethylformamide (30 ml). The mixture was heated at 60°C for 2 hours and then poured into water (500 ml). The mixture was extracted with dichloromethane (3x300 ml) and the combined extracts washed with water (8x200 ml), dried over sodium sulphate and the solvent evaporated under reduced pressure to give a red oil. Purification by flash column chromatography on silica eluting with a 3:7 mixture of ethyl acetate and petroleum ether (b.p. 40-60°C) gave (*R*)-5-[2-(2,3-epoxypropoxy)]benzo[*b*]furan-4-carboxaldehyde (3.11 g) as a yellow solid m.p. 64-65°C

3-chloroperoxybenzoic acid (85%; 3.88 g) and a solution of trifluroacetic acid (1.61 g) in dichloromethane (5 ml) were added to a stirred solution of the product from the previous reaction (3.08 g) in dichloromethane (40ml). The mixture was stirred at room temperature for 30 minutes and poured into saturated aqueous sodium bisulphite solution (200 ml) then extracted with dichloromethane (2x150 ml). The combined extracts were washed with saturated aqueous sodium bicarbonate solution (3x150 ml), dried over sodium sulphate and the solvent evaporated under reduced pressure to give (*R*)-5-[2-(2,3-epoxypropoxy)]benzo[*b*]furan-4-yl formate (3.10 g) as a red oil.

Saturated aqueous potassium carbonate solution (15 ml) was added to a stirred solution of the product from the previous reaction (3.09 g) in tetrahydrofuran (30 ml) and the mixture stirred vigorously at room temperature for 72 hours. The mixture was poured into water (200 ml) and extracted with ethyl acetate (2x150 ml). The combined extracts were dried over sodium sulphate and the solvent evaporated under reduced pressure to give an orange oil. Purification by flash column chromatography on silica eluting with a 2:3 mixture of ethyl acetate and petroleum ether (b.p. 60-80°C) gave (*S*)-2,3-dihydro-2-(hydroxymethyl)furo[3,2-*f*]-1,4-benzodioxin (1.90 g) as a pale yellow oil.

4-Toluenesulphonyl chloride (1.89 g) was added to a stirred solution of the product from the previous reaction (1.86 g) in dichloromethane (40 ml). 4-Dimethylaminopyridine (1.21 g) was then added and the resulting solution stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane (200 ml) and washed sucessively with water (100 ml), saturated copper sulphate solution (2x100 ml) and water (100 ml). The organic solution was then dried over sodium sulphate and the solvent evaporated under reduced pressure to give (*S*)-2,3-dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl 4-toluenesulphonate (3.01 g) as a colourless oil.

A mixture of the product from the previous reaction (2.80 g), potassium carbonate (10.0 g) and 1-[(2-methoxyphenyl)piperid-4-yl]methylamine (1.88 g) in dry acetonitrile (100 ml) was heated under reflux with stirring for 90 hours. The cooled mixture was filtered and the filtrate evaporated under reduced pressure to leave a pale-yellow oil. Purification by flash column chromatography on silica eluting with a 19:1 mixture of dichloromethane and methanol gave a pale-yellow oil which was then dissolved in ethanol (5 ml) and treated with a solution of fumaric acid (0.70 g) in ethanol (5 ml). The solvent was evaporated from the resulting solution under reduced pressure to give (*S*)-*N*-(2,3-dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine monofumarate monohydrate (3.06 g) as a pale-yellow solid m.p. 95-6°C, $[\alpha]_D$= - 38.5° (C=0.301, MeOH)

Example 7

A flask containing a mixture of the product fom the previous reaction (1.14 g) and pyridine hydrochloride (10 g) was submerged in a pre-heated oil bath at 180°C and the resulting solution heated with stirring at 180-200°C for 2 hours. The cooled reaction mixture was dissolved in water (200 ml), basified with aqueous ammonia, and then extracted with dichloromethane (3x100 ml). The combined extracts were washed with water (100 ml), dried over magnesium sulphate and the solvent evaporated under reduced pressure to leave a brown oil (0.90 g). Purification by flash column chromatography on silica eluting with a 19:1 mixture of dichloromethane and methanol gave a pale orange oil (0.23 g). A portion of this oil (0.2 g) was dissolved in ethanol (1 ml) and then treated with a solution of fumaric

acid (60 mg) in ethanol (5 ml). The resulting solution was evaporated under reduced pressure to give (S)-2-{4-[(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-aminomethyl]piperidino}phenol monofumarate 1.1 hydrate, 0.25 ethanol solvate (0.27g) as an orange solid m.p. 88-9°C, $[\alpha]_D$= - 37.7° (C= 0.257, EtOH)

Example 8

A solution of 3,4-methylenedioxyphenol (40 g) in diethyl ether (350 ml) was added dropwise to a stirred suspension of sodium hydride (12.9 g) in a mixture of dimethylformamide (110 ml) and diethyl ether (470 ml) at room temperature. The mixture was stirred until the evolution of hydrogen had ceased, then a solution of diethyl carbamoyl chloride (47 g) in diethyl ether (110 ml) was added and the mixture was stirred for 1 hour, then left to stand at room temperature for 17 hours.

The reaction mixture was poured into water (600 ml) and the product was extracted with diethyl ether (3 x 300 ml). The ethereal layers were combined, washed with 10% aqueous sodium hydroxide solution (2 X 200 ml), dried over magnesium sulphate and evaporated under reduced pressure to give 3,4-methylenedioxyphenyl *N,N*-diethylcarbamate (59 g) as a white solid.

N,N,N',N'-Tetramethylethylenediamine (4 ml) was added to a stirred solution of sec-butyllithium (1.3 M solution in cyclohexane; 21ml) in tetrahydrofuran (25 ml) at -78°C. The mixture was stirred for 30 minutes then added via a cannula to a stirred solution of the product from the previous reaction (5 g) in tetrahydrofuran (70 ml) at -78°C. The mixture was stirred for 2 hours and then dimethylformamide (10 ml) was added. The reaction mixture was allowed to warm to room temperature over 1 hour and the resulting deep red solution was poured into saturated aqueous ammonium chloride solution (500 ml) and extracted with diethyl ether (3 x 200 ml). The combined extracts were dried over magnesium sulphate, and the solvent was evaporated under reduced pressure to leave a brown oil. Purification by flash column chromatography on silica eluting with a 9:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate afforded 5,6-methylenedioxysalicaldehyde (1.1 g) as a yellow solid.

A mixture of potassium carbonate (2.8 g), 5,6-methylenedioxysalicaldehyde, prepared by the method given above, (3.1 g) and (*R*)-glycidyl tosylate (4.2 g) in dimethylformamide (85 ml) was stirred and heated at 60°C under an atmosphere of nitrogen for 18 hours. The mixture was poured into water (700 ml) and extracted with diethyl ether (4 x 300 ml). The combined extracts were washed with brine (3 x 400 ml), dried over magnesium sulphate and the solvent evaporated under reduced pressure. The yellow solid residue was purified by flash column chromatography on silica eluting with a 2:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate to give (*R*)-2-(2,3-epoxypropoxy)-5,6-methylenedioxybenzaldehyde (1.6 g) as a pale yellow solid.

A stirred solution of the product from the previous reaction (1.5 g) and 3-chloroperoxybenzoic acid (56-87%; 4.3 g) in dichloromethane (100 ml) was stirred and heated at reflux temperature for 6.5 hours then left to stand at room temperature for 72 hours. More 3-chloroperoxybenzoic acid (56-87%; 1 g) was then added and the solution was heated for a further 2 hours. The mixture was allowed to cool, washed with saturated aqueous sodium bicarbonate solution (4 x 400 ml), water (2 x 400 ml), brine (2 x 400 ml) and dried over magnesium sulphate. The solvent was evaporated under reduced pressure to afford crude (*R*)-2-(2,3-epoxypropoxy)-5,6-methylenedioxyphenyl formate (1 g) as a red oil.

Saturated aqueous potassium carbonate solution (13 ml) was added to a solution of the product from the previous reaction (1 g) in tetrahydrofuran (16 ml) and the mixture was stirred at room temperature for 18 hours. The mixture was poured into water (100 ml) and extracted with ethyl acetate (3 x 60 ml). The combined extracts were dried over magnesium sulphate and the solvent evaporated under reduced pressure to give a brown oil. Purification by flash column chromatography on silica eluting with a 2:1 mixture of petroleum ether (b.p. 40-60°C) and ethyl acetate afforded (*S*)-7,8-methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethanol (0.3 g) as a clear oil.

A solution of 4-toluenesulphonyl chloride (0.29 g) in dichloromethane (10 ml) was added dropwise to a stirred solution of the product from the previous reaction (0.3 g) and 4-dimethylaminopyridine (0.21 g) in dichloromethane (10 ml) at 0-5°C. The mixture was allowed to warm to room temperature and stirred for 18 hours. The

solution was diluted with dichloromethane (30 ml) and washed successively with water (100 ml), dilute aqueous hydrochloric acid (5M, 3 x 100 ml), brine (2 x 100 ml) and then dried over magnesium sulphate. Evaporation of the solvent under reduced pressure gave (*S*)-7,8-methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl 4-toluenesulphonate (0.45 g) as a colourless solid.

A mixture of the product from the previous reaction (0.45 g), potassium carbonate (0.32 g) and 1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (0.51 g) in dimethylformamide (4.5 ml) and toluene (10 ml) was heated at reflux temperature for 6 hours, then left to stand at room temperature for 72 hours and then heated at reflux temperature for a further 4 hours. The cooled mixture was poured into water (300 ml) and extracted with ethyl acetate (3 x 40 ml). The combined organic extracts were extracted with dilute aqueous hydrochloric acid (5M; 3 x 30 ml) and the combined aqueous extracts basified by the addition of sodium hydroxide solution (5M). The aqueous phase was extracted with ethyl acetate (3 x 300 ml), dried over magnesium sulphate and the solvent removed under reduced pressure to yield a yellow oil. Purification by flash column chromatography on silica eluting with a 95:5 mixture of ethyl acetate and methanol afforded (*S*)-*N*-(7,8-methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (0.3 g) as a clear oil. Citric acid (0.14 g) in ethanol (20 ml) was added to a solution of the oil in ethanol (20 ml) and the solvent was removed under reduced pressure to afford (*S*)-*N*-(7,8-methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methyl- amine monocitrate (0.3 g) as a fawn solid; m.p 120-22°C, $[\alpha]_D$ -35.9°(c=0.575,MeOH)

Example 9

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

c) Enteric coated tablets

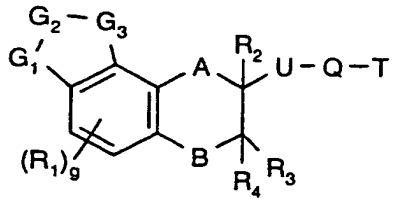
Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

Claims

1) Compounds of formula I



I

including pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers, in which

A is methylene or -O-;

B is methylene or -O-;

G_1-G_2-G_3 represent -N(R′)-C(R″)=N-, -N=C(R″)-N(R′)-, -N(R′)-C(R″)=C(R‴)-, -C(R‴)=C(R″)-N(R′)-, -N(R′)-N=C(R″)-, -C(R″)=N-N(R′)-, -N(R′)-N=N-, -N=N-N(R′)-, -N=C(R″)-O-, -N=C(R″)-S-, -O-C(R″)=N-, -S-C(R″)=N-, -O-N=C(R″)-, -S-N=C(R″)-, -C(R″)=N-O-, -C(R″)=N-S-, -S-C(R″)=C(R‴)-, -C(R″)=C(R‴)-S-, -O-C(R″)=C(R‴)-, -C(R″)=C(R‴)-O- or -O-C(R′)(R′)-O- wherein

R′ is H or an alkyl group containing 1 to 3 carbon atoms; and

R″ and R‴, which are the same or different, are H; halo; an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; carboxy; an alkanoyl group containing 1 to 6 carbon atoms; an alkoxycarbonyl group in which the alkoxy group contains 1 to 3 carbon atoms; formyl; cyano; or a carbamoyl group or carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups, which may be the same or different, each containing 1 to 3 carbon atoms;

g is 0, 1 or 2;

R_1 represents an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo; an alkoxy group containing 1 to 3 carbon atoms optionally

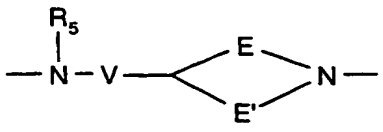
substituted by one or more halo; halo; or an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo; the substituents represented by R_1 being the same or different when g is 2;

R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

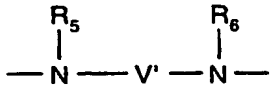
R_3 and R_4, which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

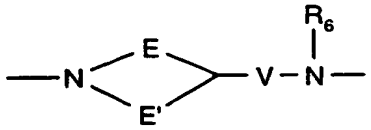
Q represents a divalent group of formula IIa, IIb or IIc



IIa



IIb



IIc

in which V is $(CH_2)_n$, wherein n is 0, 1, 2 or 3, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

V' is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

E is an alkylene chain containing 0 to 2 carbon atoms and E' is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in E and E' amounts to 3 or 4; and

R_5 and R_6, which may be the same or different, are H or an alkyl group containing 1 to 4 carbon atoms; and

T represents phenyl, 1- or 2-naphthyl, 1-naphth[2,1-*d*][1,2,3]oxadiazolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2- or 3-thienyl, 2- or 3-furyl, 2-, 3- or 7-benzo[*b*]furanyl, 2,3-dihydro-7-benzo[*b*]furanyl, 2-, 3- or 7-benzo[*b*]thiophenyl, 3-, 4- or 5-pyrazolyl, 1,2,3-triazol-4-yl, 1,2,3-triazol-5-yl, 1,2,4-triazol-2-yl, 5-tetrazolyl, 2-, 3- or 4-quinolinyl, 2- or 4-quinazolinyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl or 2-, 4- or 5-thiazolyl each of which may be optionally substituted by one or more substituents selected from a) halo, b) an alkyl group containing 1 to 4 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally *N*-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 5 carbon atoms, n) 1-pyrrolidinyl or 1-piperidinyl, o) nitro or p) acetamido.

2) Compounds as claimed in claim I in which both A and B are -O-.

3) Compounds as claimed in either claim 1 or claim 2 in which g is 0 or 1.

4) Compounds as claimed in any preceding claim in which R_1 is halo or an alkyl group containing 1 to 3 carbon atoms.

5) Compounds as claimed in any preceding claim in which G_1-G_2-G_3 are -N(R′)-C(R″)=C(R‴)-; -S-C(R″)=C(R‴)-, -N(R′)-N=C(R″)-,. -O-C(R″)=C(R‴)-, or -O-C(R′)(R′)-O-

6) Compounds as claimed in any preceding claim in which R_2 is H.

7) Compounds as claimed in any preceding claim in which R_3 and R_4, are both H.

8) Compounds as claimed in any preceding claim in which U is methylene.

9) Compounds as claimed in any preceding claim in which Q is a group of formula IIa in which V is methylene, E and E′ are both ethylene and R_5 is H.

10) Compounds as claimed in any preceding claim in which T is phenyl or naphthyl, each of which may be optionally substituted by one or more substituents selected from an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or halo.

11) Compounds as claimed in any preceding claim in which G_1-G_2-G_3 are -O-CH=CH-.

12) Compounds of formula I, as claimed in claim 1, selected from:

N-(9-Chloro-2,3-dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(2,3-Dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

Ethyl 2,3-dihydro-2-(*N*-{[1-(2-methoxyphenyl)piperid-4-yl]methyl}aminomethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate;

N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indazol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

2-{4-[(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)aminomethyl]piperidino}-phenol;

N-(7,8-Methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

13) Compounds of formula I as claimed in claim 1 selected from

(*S*)-*N*-(9-Chloro-2,3-dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(*S*)-N-(2,3-Dihydrothieno[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl) piperid-4-yl]methylamine;

Ethyl (*S*)-2,3-dihydro-2-(*N*-{[1-(2-methoxyphenyl)piperid-4-yl]methyl}aminomethyl)-7*H*-1,4-dioxino[2,3-*e*]indole-8-carboxylate;

(*S*)-N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indol-2-ylmethyl)-1-[1-(2-methoxyphenyl)-piperid-4-yl]methylamine;

(*S*)-N-(2,3-Dihydro-7*H*-1,4-dioxino[2,3-*e*]indazol-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine

(*S*)-*N*-(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine

(S)-2-{4-[(2,3-Dihydrofuro[3,2-*f*]-1,4-benzodioxin-2-ylmethyl)aminomethyl]-piperidino}phenol;

(*S*)-*N*-(7,8-Methylenedioxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine

and pharmaceutically acceptable salts thereof.

14) A pharmaceutical composition comprising a compound of formula I, as claimed in any one of claims 1-13, in conjunction with a pharmaceutically acceptable diluent or carrier.

15) A compound of formula I, as claimed in one of claims 1-13, for use as a medicament.

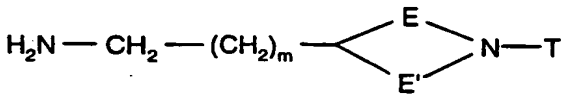
16) A compound of formula I, as claimed in any one of claims 1-13, for use in the treatment of depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, and spasticity.

17) A compound of formula I, as claimed in claim 16, for use in the treatment of psychoses.

18) Use of a compound of formula I, as claimed in any one of claims 1-13, in the manufacture of a medicament for treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity.

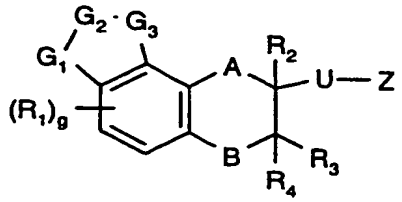
19) A method of treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, social phobias, eating disorders and anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, or spasticity in human beings, which comprises the administration of a therapeutically effective amount of a compound of formula I, as claimed in any one of claims 1-13, to a patient in need thereof.

20) A process for the preparation of compounds of formula I, as claimed in claim 1, in which Q is a group of formula IIa, comprising the reaction of a compound of formula III



III

in which m is 0, 1 or 2, with a compound of formula IV



IV

in which Z is a leaving group, optionally in the presence of a base, and optionally in a solvent.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 98/00946

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D495/04 C07D491/04 A61K31/40 A61K31/415 C07D493/04
//(C07D495/04,333:00,319:00),(C07D491/04,319:00,209:00),
(C07D491/04,319:00,231:00),(C07D493/04,319:00,307:00),
According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	EP 0 771 800 A (AMERICAN HOME PRODUCTS CORPORATION;USA) 7 May 1997 see definitions of Z and pharmaceutical activity ---	1-18,20
Y	ENNIS M D ET AL: "Novel indolodioxanes with antihypertensive effects: potent ligands for the 5-HT1A receptor" J. MED. CHEM. (JMCMAR,00222623);92; VOL.35 (16); PP.3058-66, UPJOHN CO.;DEP. MED. CHEM.; KALAMAZOO; 49001; MI; USA (US), XP002067939 see compound 23, Table I and activity Table II --- -/--	1-18,20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 1998	09/07/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/EP 98/00946

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (C07D493/04,319:00,317:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	WO 91 13872 A (UPJOHN CO.;USA) 19 September 1991 see the definitions of X, particularly b), with R3 as NHR2 and R2 as (CH2)mAr and the whole document, especially example XIi on page 24	1-18,20
Y	WO 95 07274 A (THE BOOTS COMPANY PLC) 16 March 1995 cited in the application see the whole document, especially pages 32-40 and examples	1-18,20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
15 June 1998	

Name and mailing address of the ISA	Authorized officer
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2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP 98/00946

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N-Substituted (2,3-Dihydro-1,4-benzodioxin-2-yl)methylamine Derivatives as D_2 Antagonists/5-HT_{1A} Partial Agonists with Potential as Atypical Antipsychotic Agents

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A series of *N*-substituted 1-(2,3-dihydro-1,4-benzodioxin-2-yl)methylamine derivatives with D_2 antagonist/5-HT_{1A} partial agonist activity has been prepared as potential atypical antipsychotic agents. Optimization of in vitro receptor binding activity and in vivo activity in rodent models of psychosis has led to compound **24**, which showed good affinities for human D_2, D_3, and 5-HT_{1A} receptors but significantly less affinity for human α_1 adrenoceptors and rat H_1 and muscarinic receptors. In rodents, **24** showed functional D_2-like antagonism and 5-HT_{1A} partial agonism. After oral dosing, **24** showed good activity in rodent antipsychotic tests and very little potential to cause extrapyramidal side effects (EPS), as measured by its ability to induce catalepsy in rats only at very high doses. In the light of this promising profile of activity, **24** has been selected for clinical investigation as a novel antipsychotic agent with a predicted low propensity to cause EPS.

Introduction

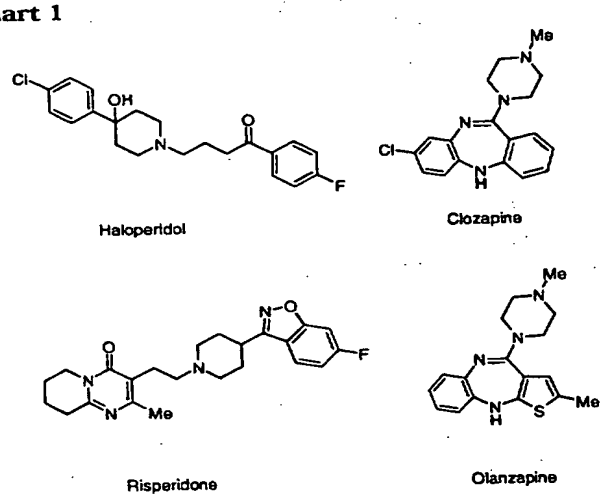
Schizophrenia is a relatively common disorder, affecting approximately 1% of the population, and one where established therapies leave much room for improvement. Progress is still sought in terms of efficacy, against both the positive symptoms of the disease, such as delusions and hallucinations, and the negative symptoms, such as social withdrawal and flattened affect, and also in terms of lower side effect potential. There is strong evidence[1] that classical antipsychotic agents, such as haloperidol (Chart 1), exert their beneficial effects through blockade of central dopamine D_2 receptors. In addition, the acute extrapyramidal side effects (EPS) induced by these agents, such as Parkinsonism, akathisia, and dystonia, are also thought to result from their high degree of D_2-receptor antagonism.

Clozapine is exceptional among established antipsychotic agents, as it combines effectiveness against both positive and negative symptoms of the disease with a very low propensity to induce EPS. It has significant affinity for a broad range of neurotransmitter receptors,[2] which seems to account for its clinical effectiveness at a relatively low occupancy of D_2 receptors (40−60%),[1] which in turn is probably responsible for the lack of EPS seen with the drug. Clozapine was withdrawn from the market over 20 years ago due to a relatively high incidence of potentially fatal agranulocytosis, but was reintroduced more recently, under carefully controlled conditions, for the treatment of patients who failed to respond to other drugs.

The search for alternatives to clozapine, which match its effectiveness but lack its serious side effects, has led to the structurally related compounds zotepine,[3] olanzapine,[4] and quetiapine,[5] which are all newly approved for the treatment of schizophrenia in major markets. An alternative approach to the discovery of atypical antipsychotics has been to target the other newly identified dopamine receptor subtypes, e.g., D_1/D_5, D_3, and D_4, which would not be expected to be associated with EPS.[1] However, although a number of selective, high-affinity compounds have been described, none of these has yet been reported to be clinically effective. More successful has been the combination of D_2-receptor antagonism with serotonergic activity. For example, in the recently introduced drugs risperidone[6] and sertindole,[7] 5-HT_{2A}-receptor antagonism is believed to play an important role in their activity.

Typical D_2-receptor antagonists, such as haloperidol and raclopride, induce catalepsy in rats, an activity which is predictive of the propensity of compounds to cause EPS when administered to man. Following the demonstration that the 5-HT_{1A}-receptor full agonist 8-hydroxy-2-(dipropylamino)tetralin (8-OH-DPAT) reversed this catalepsy,[8] we sought to find molecules which combined antagonism at D_2-like receptors with agonism or partial agonism at 5-HT_{1A} receptors. We required these compounds to have much lower affinity

Chart 1



10.1021/jm9910122 CCC: $18.00
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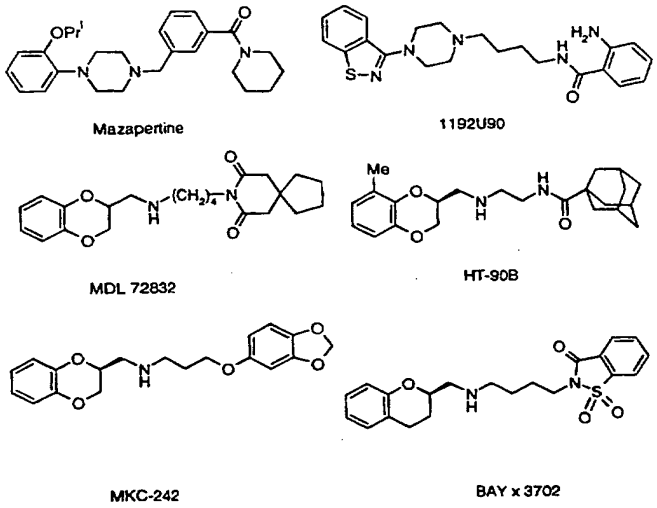
Chart 2



for receptors associated with side effects, such as α_1 adrenoceptors (sedation, postural hypotension), histamine H_1 (sedation), and muscarinic (dry mouth, blurred vision).

Other research groups have also targeted D_2-antagonist/5-HT_{1A}-agonist compounds as potential antipsychotics with low EPS. At least two such compounds, RWJ-37796 (mazapertine, Chart 2)[9] and 1192U90[10] have reached early clinical development. These two compounds are arylpiperazine derivatives which show high and approximately equal affinities for D_2, 5-HT_{1A}, and α_1 receptors. The clinical undesirability of high affinity for α_1 adrenoceptors was reinforced by reports that mazapertine[11,12] had encountered problems with postural hypotension in clinical trials.

The arylpiperazine moiety found in the compounds above would appear to be isosteric with the *N*-(2,3-dihydro-1,4-benzodioxin-2-yl)methylamine substructure, as evidenced by accounts of several derivatives of the latter type which also have activity at various dopaminergic, serotoninergic, and noradrenergic receptor subtypes. Often, compounds of this type show significant affinity for D_2, 5-HT_{1A}, and α_1 receptors, although the relative proportion varies with the particular structural class. For example, the spirocyclic imide derivatives such as MDL 72832 and its aza-analogues[13] show selectivity for the 5-HT_{1A} receptor, though with still significant affinities for D_2 and α_1 receptors. Comparison of the enantiomers of MDL 72832 with other standard 5-HT_{1A} ligands, using molecular modeling techniques,[14] allowed Hibert and co-workers to derive a pharmacophore for that receptor. The model correctly predicted that the (*S*)-enantiomer would have the higher affinity. The 8-methyl-2,3-dihydro-1,4-benzodioxin derivative (−)HT-90B is structurally related to the compound above and shares a similar profile, with some selectivity for 5-HT_{1A} but still significant affinities for D_2 and α_1 receptors.[15] MKC-242 is another benzodioxin derivative, and although it lacks a polar amide group in its side chain, its receptor binding profile remains similar.[16]

In contrast to these, a series of 7-hydroxy-2,3-dihydrobenzodioxin derivatives, together with their chroman and tetralin analogues, were found to show some preference for the D_2 receptor (high-affinity form) and to show agonist properties.[17] Again the (*S*)-(−)-forms showed the higher affinities.

The chroman derivative BAY x 3702 is, in general structural terms, similar to MDL 72832 and is also a potent 5-HT_{1A} ligand with some selectivity over α_1 and D_2.[18] A recent report describes aminotetralin derivatives, which may be regarded as hybrid structures between 8-OH-DPAT and the amides described above, as having more balanced affinities for 5-HT_{1A} and D_2 receptors.[19]

We report here a new series of *N*-substituted 1-(2,3-dihydro-1,4-benzodioxin-2-yl)methylamine derivatives, the best of which have good affinity and selectivity for the D_2 and 5-HT_{1A} receptors and show potential for atypical antipsychotic activity in animal models.

Chemistry

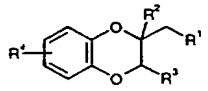
The majority of the target compounds described in this study (Table 1) were prepared either directly or indirectly by reaction of the (2,3-dihydro-1,4-benzodioxin-2-yl)methyl tosylates **25** with various amine nucleophiles **26** as depicted in Scheme 1. The (2,3-dihydro-1,4-benzodioxin-2-yl)methyl tosylates **25a−e** were synthesized by tosylation of the known (2,3-dihydro-1,4-benzodioxin-2-yl)methanols **27a−e**, which were obtained from commercial sources or by preparation as described in the literature.[20−23] Tosylates **25h,i** were prepared from the methanols **27h,i**, which were in turn obtained from the corresponding esters **28a,b** by reduction with $LiAlH_4$. The esters **28a,b** were initially prepared as a mixture by literature methods.[24] To separate the two regioisomers, the mixture was converted into the carboxamides **29a,b**, which were separated by fractional crystallization and then alcoholized back to the individual esters (Scheme 2).

The remaining tosylates **25f,g** were obtained by the synthetic route outlined in Scheme 3. This involved alkylation of the substituted salicylaldehydes **30a,b** with (*R*)-glycidyl tosylate to give the ethers **31a,b** and then subsequent Baeyer−Villiger oxidation to give the formate esters **32a,b**. Alkylations of this type are known to proceed predominantly with retention of configuration at the glycidyl asymmetric center,[25] thus leading to the (*S*)-(2,3-dihydro-1,4-benzodioxin-2-yl)methanols. This stereochemical course was confirmed for the final product **24** by X-ray crystallographic studies[26] which showed it to have the *S*-stereochemistry. All other levorotatory final products are assumed, therefore, to share the *S*-stereochemistry.

Treatment of **32a,b** with sodium methoxide in methanol resulted in cleavage of the formate ester and concomitant cyclization, yielding the (2,3-dihydro-1,4-benzodioxin-2-yl)methanols **27f,g**. Finally, reaction with tosyl chloride in pyridine gave the tosylates **25f,g** in good yield.

The intermediate amines **26a−i** were synthesized by the route described in Scheme 4. Reaction of 1-chloro-2,4-dinitrobenzene with isonicotinamide at 95 °C, in the absence of solvent, led to the formation of the pyridinium salt **33**, which on amine exchange[27] gave the pyridinium salts **34a−g**. Subsequent reduction of the pyridine ring was accomplished using H_2 on Pd/C, affording piperidines **35a−g**. Finally, reduction with $LiAlH_4$ furnished the key amines **26a−g**.

Table 1. Structures and Comparative in Vitro and in Vivo Activities for Target and Standard Compounds



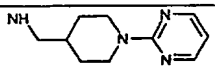
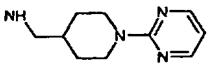
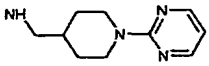
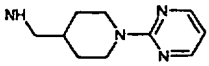
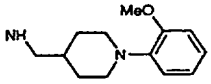
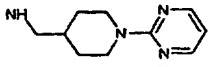
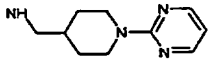
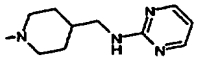
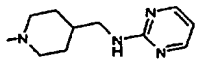
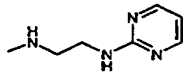
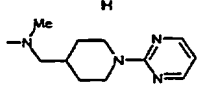
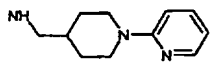
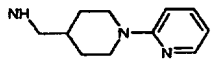
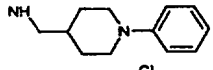
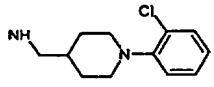
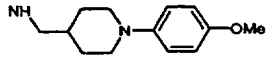
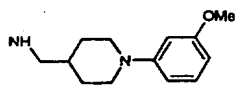
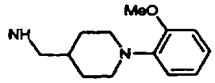
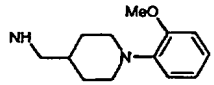
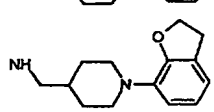
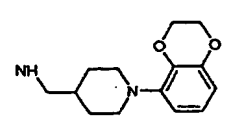
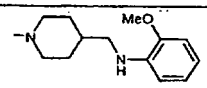
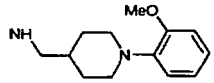
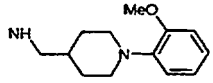
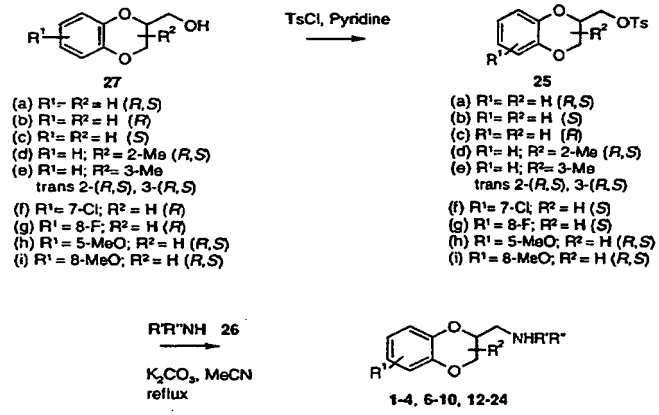
	Compound	R^1	R^2	R^3	R^4	D_2-like[a]	5-HT_{1A}[b]	α_1[b]	AC[c]	CAT[d]
1	(*S*)-(-)		H	H	H	26	2.7 ± .3	18 ± 3	9	44
2	(*R*)-(+)		H	H	H	59	25 ± 1.8	117 ± 19	77%@50 mg/kg	NT
3	(*R,S*)		H	H	8-OMe	7.6	0.6 ± .1	2.3 ± .1	2.4	NT
4	(*R,S*)		H	H	5-OMe	64	128 ± 14	234 ± 29	NT	NT
5	(*R,S*)		H	H	8-OH	25	94%	>500	33	NT
6	(*R,S*)		Me	H	H	97	195 ± 23	132 ± 15	NT	NT
7	2-(*R,S*)-3-(*R,S*)		H	Me	H	113	>500	>500	134	775
8	(-)		H	H	H	6.9	21± 3.3	23 ± 2	NT	NT
9	(+)		H	H	H	112	463 ± 41	208 ± 39	NT	NT
10	(*R,S*)		H	H	H	16	3.1 ± 4.2	16 ± 2	6	NT
11	(*S*)		H	H	H	260	85%	348 ± 3	NT	NT
12	(-)		H	H	H	24	98%	98%	23	NT
13	(+)		H	H	H	27	82%	84%	55%@50 mg/kg	NT
14	(*R,S*)		H	H	H	39	29 ± 3.3	47 ± 5	39	NT
15	(*R,S*)		H	H	H	30	17 ± 2.1	94 ± 16	IA @ 10 mg/kg	NT
16	(*R,S*)		H	H	H	36	15 ± 2.4	44 ± 4	11 (duration 2h)	NT
17	(*R,S*)		H	H	H	54	7 ± 2	35 ± 4	45% @ 50 mg/kg	NT
18	(*S*)-(-)		H	H	H	26	8 ± 1.9	23 ± 2	7 (duration 3.5 h)	50
19	(*R*)-(+)		H	H	H	64	37 ± 7.6	74 ± 6	38	NT
20	(*R,S*)		H	H	H	31	3 ± .3	33 ± 4	18 (duration 2 h)	107
21	(*R,S*)		H	H	H	23	18 ± 4.5	38 ± 6	32 (duration 6h)	>200

Table 1 (Continued)

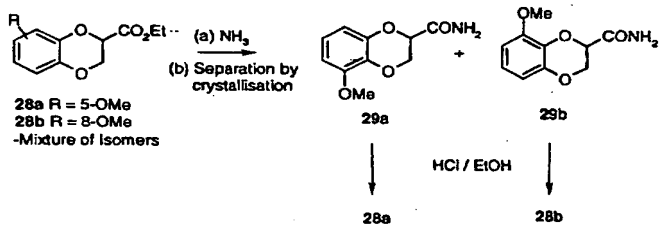
Compound		R^1	R^2	R^3	R^4	D_2-like[a]	5-HT_{1A}[b]	α_1[b]	AC[c]	CAT[d]
22	(*R,S*)		H	H	H	69	20 ± 1.3	20 ± 3	62	NT
23	(*S*)-(-)		H	H	8-F	28	16 ± .2	12 ± 4.7	4 (duration 4h)	23
24	(*S*)-(-)		H	H	7-Cl	44	22 ± 3.7	53 ± 3	5 (duration >6h)	188
haloperidol						2.2	>500	5.7 ± 1.2	0.16	0.44
risperidone						5.1	720 ± 22	1.0 ± .1	0.30	1.75
clozapine						359	415 ± 33	11 ± .9	9.5	33.9
olanzapine						15.7	>500	14 ± 1.2	4.87	6.07

[a] K_i values (nM). Values are from single experiments where dose–response curves were determined with at least six concentrations of compound, and each displacement was measured in triplicate. [b] K_i values (nM) ± SEM. Percentages are for displacement of radioligand at 10^{-6} M. [c] ED_{50} values (mg/kg po) for antagonism of apomorphine-induced climbing in the mouse. Percentages are for reduction in climbing at dose given. Duration is defined by the time at which level of climbing has returned to 50% of control following a dose of 2 × ED_{50}. [d] ED_{50} values (mg/kg ip) for induction of catalepsy in the rat. IA, inactive—causing <50% reduction of climbing at highest dose; NT, not tested.

Scheme 1



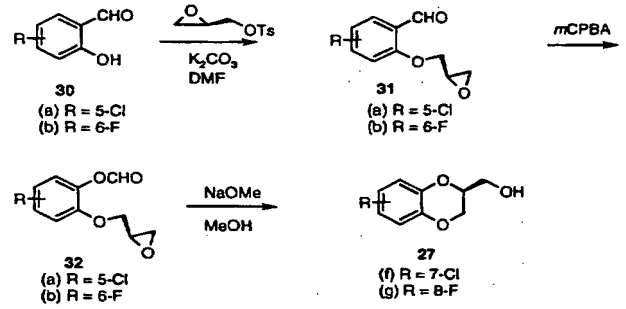
Scheme 2



The amine **26h** was prepared by direct reaction of 2-chloropyridine with 4-(aminomethyl)piperidine **36a**, whereas amine **26i** was prepared from 2-chloropyrimidine and the imine **36b** followed by acid hydrolysis, as depicted in Scheme 4.

In the pyrimidine series, analogues in which the bridging aminomethylpiperidine group was reversed were prepared by reaction of tosylate **25a** with the protected amine **45**, followed by hydrolysis to the primary amine and reaction with 2-chloropyrimidine (Scheme 5). Preparative chiral HPLC then gave enantiomers **8** and **9**. The corresponding 2-methoxyphenyl analogue was prepared by alkylation of ethyl 4-piperidinecarboxylate with 2-(chloromethyl)-2,3-dihydro-1,4-benzodioxin, giving the ester **37**, which on base hydrolysis gave the carboxylic acid **38**. Subsequent mixed anhydride formation with ethyl chloroformate and reaction with 2-methoxyaniline gave the amide **39**, which was reduced with borane-dimethyl sulfide complex to furnish the target compound **22** (Scheme 6).

Scheme 3



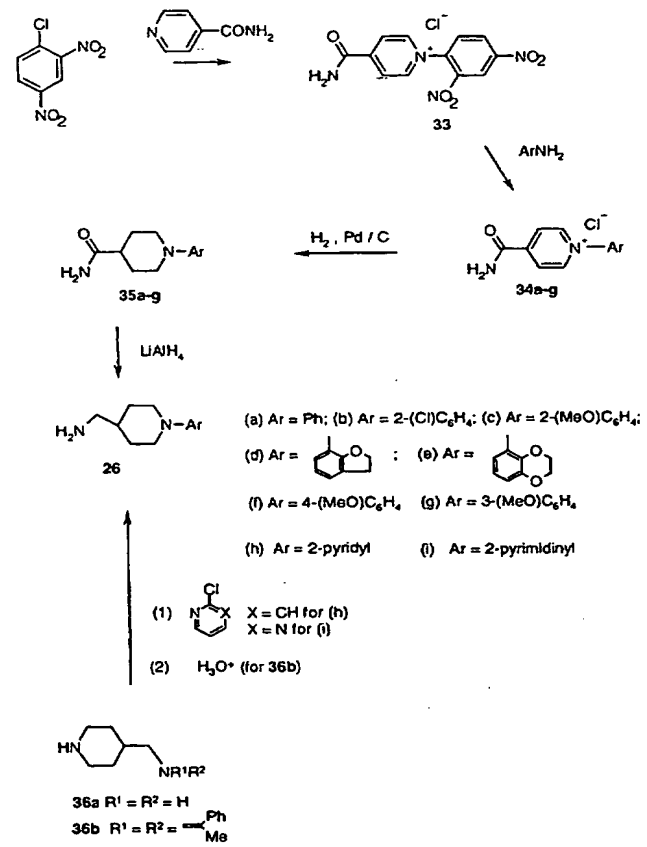
The open-chain analogue **10** was synthesized by the route described in Scheme 7. Reduction of 2,3-dihydro-1,4-benzodioxin-2-carbonitrile with $LiAlH_4$ afforded the methylamine **40** which, when reacted with *N*-(3-bromopropyl)phthalimide, gave intermediate **41**. Subsequent cleavage of the phthalimide group with hydrazine produced the primary amine **42**, which upon reaction with 2-chloropyrimidine gave a mixture of the desired target compound **10** and the bis(2-pyrimidinyl) derivative **43**.

Compound **11** was prepared in 46% yield by direct methylation of **1** using a mixture of sodium formate, formaldehyde, and formic acid. The 8-hydroxy derivative **5** was prepared by hydrolysis of the corresponding 8-tosyloxy compound **49** (itself obtained via ditosylate **48**) using potassium hydroxide in ethanol (Scheme 8).

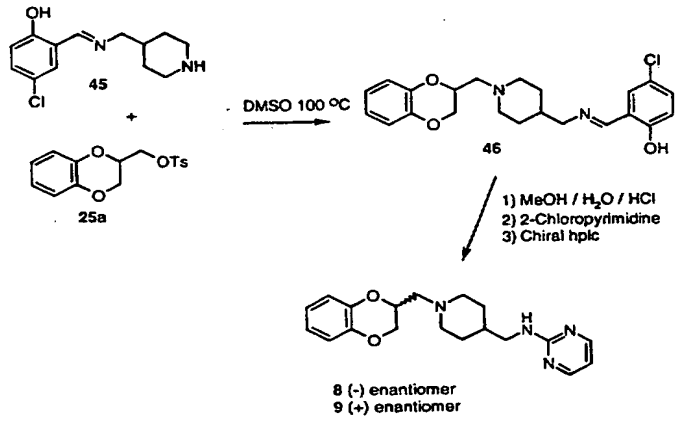
Biological Results

Compound library screening gave the lead *N*-substituted (2,3-dihydro-1,4-benzodioxin-2-yl)methylamine derivative **1** and its enantiomer **2**, originally prepared for another CNS project, which showed moderate to good

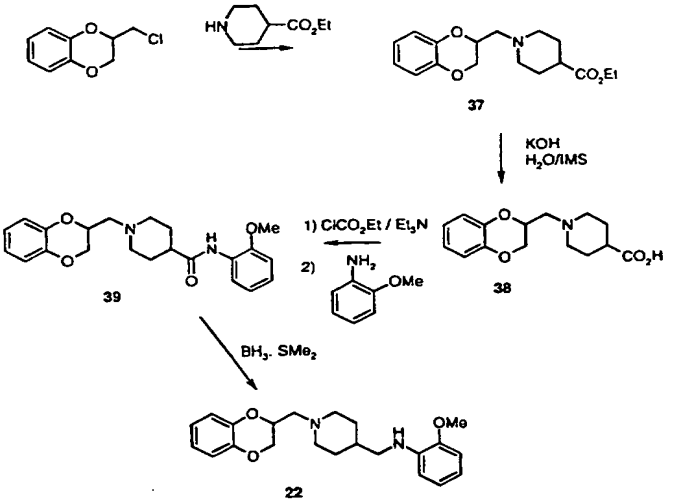
Scheme 4



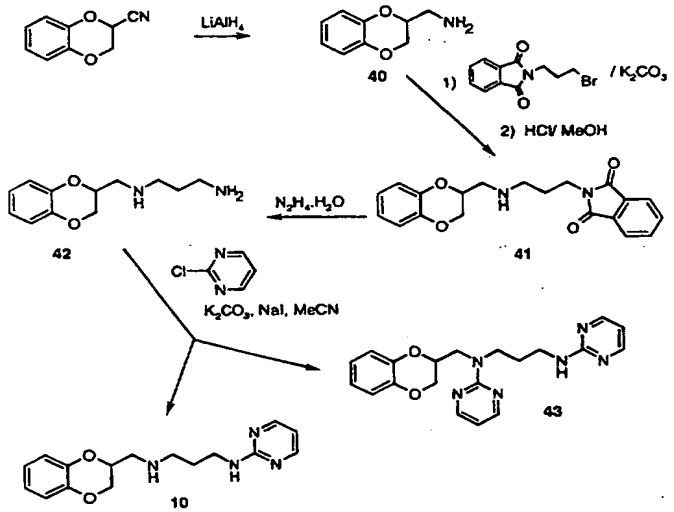
Scheme 5



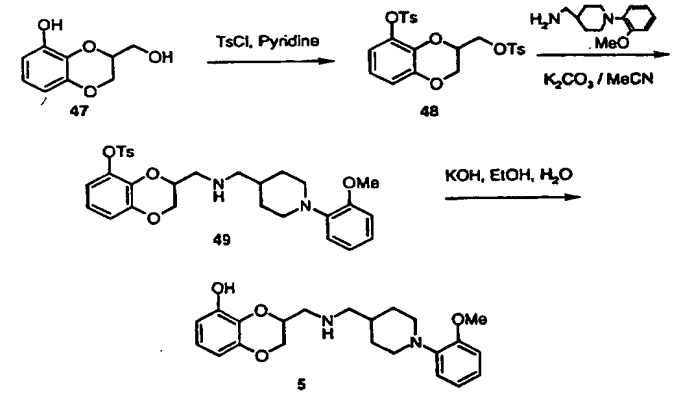
Scheme 6



Scheme 7



Scheme 8



affinities for rat D_2-like and 5-HT_{1A} receptors, with the (−)-isomer **1** being the more active (Table 1). Compound **1** also showed moderate activity in the mouse apomorphine climbing test (AC), a model of antipsychotic activity, having an ED_{50} of 9 mg/kg after oral administration. The (+)-isomer was less active, giving a 77% reduction in climbing at 50 mg/kg.

Further in vivo profiling of **1**, in the two-component amphetamine stereotypy test,[3] showed the compound to be approximately equipotent in antagonizing the effects of amphetamine-induced dopamine release in the limbic and striatal regions of rat brain (ED_{50} values of 2 mg/kg and 1.5 mg/kg, respectively). This indicates that the relative lack of EPS potential shown by **1** (see below) does not result from selective attenuation of postsyn aptic dopamine receptor function in the limbic area o the brain.

Compound **1** caused a relatively weak induction o catalepsy[3] in rats, the ED_{50} value (Table 1) being 2 times greater than that for antagonism of the limbi amphetamine-induced locomotion effects. At 30 mg/k

1 caused a significant 20% reduction in mouse brain levels of the 5-HT precursor 5-HTP, indicating that the compound has agonist activity at 5-HT_{1A} receptors.

As the classical antipsychotic haloperidol, a D_2-like antagonist with little or no 5-HT_{1A} receptor affinity, induces catalepsy in rats with an ED_{50} of only 4 times greater than that in the limbic amphetamine-induced locomotion test, the results for **1** strongly suggested that combining D_2-like antagonism with 5-HT_{1A} (partial) agonism in a single molecule would give effective antipsychotic compounds with a reduced propensity to induce extrapyramidal side effects.

The relatively high α_1 affinity of **1** was seen as a shortcoming, as this would be likely to lead to unwanted cardiovascular effects, including postural hypotension. In addition to reduced α_1 affinity, greater potency in vivo and a further reduction in cataleptic potential were also considered desirable. A further requirement for a development compound was that it should have the potential for once or twice daily dosing in man. As a predictor of this, greater than 6 h duration (see Table 1 for definition) would be required in the AC test. Therefore, further analogues of compound **1** were prepared in order to address these concerns.

Substitution in the aromatic ring of the dihydrobenzodioxin system was not explored extensively in this pyrimidine-containing subseries, although 5- and 8-methoxy substituents were found to have opposite effects on receptor affinity. The racemic 8-methoxy compound **3** had significantly higher affinity for D_2-like, 5-HT_{1A}, and α_1 receptors than **1**, and it was correspondingly more active in AC. The 5-methoxy compound **4**, in contrast, had much reduced affinity for these three receptors. The 8-hydroxy compound **5** also had good affinity for D_2-like and 5-HT_{1A} receptors, but was only weakly active in AC.

Introduction of a methyl substituent into the 2- or 3-position of the dihydrobenzodioxin system, as in compounds **6** and **7**, led to significant loss of receptor affinities.

Reversal of the bridging 4-(aminomethyl)piperidine grouping found in **1** gave the enantiomers **8** and **9**, which showed receptor binding profiles similar to **1** and **2**, respectively. Incorporation of an acyclic bridge, as in the racemate **10**, also led to activity similar to that of **1**, both in receptor affinities and in AC activity.

N-Methylation of **1**, to give the tertiary amine **11**, led to significant loss of receptor affinities.

It seemed at this point that neither substituent variation in the benzodioxin ring nor alternative configurations of the bridging portion of the side chain would give us the potency and selectivity we required. Alternatives to the 2-pyrimidinyl grouping were therefore explored, in the form of the 2-pyridyl containing enantiomers **12** and **13**, and the phenyl and 2-chlorophenyl containing racemates **14** and **15**. Although receptor affinities were maintained, activity in AC was moderate at best. It was not clear which of many potential factors, including degree of functional activity at D_2 and 5-HT_{1A} receptors and bioavailability, were adversely affecting the in vivo activity of these compounds, but it seemed worthwhile to try to mimic the H-bond acceptor properties of the pyrimidines with alkoxyphenyl groups. Thus, the 4-, 3-, and 2-methoxyphenyl analogues **16**–**19** were found to show similar binding profiles, with the 4- and 2-isomers showing significant in vivo activity. The (−)-enantiomer **18** of the 2-methoxy compound showed acceptable potency and duration of action in the AC test. This compound also showed good activity in antagonizing limbic amphetamine-induced stereotypy (ED_{50} 4.4 mg/kg), combined with only a moderate ability to induce catalepsy. The corresponding (+)-isomer **19** was again less active both in vitro and in vivo.

A concern with the methoxy substituted compounds was their propensity for metabolic demethylation, which could have adverse effects on the compound's pharmacokinetics. Investigation of heterocyclic alternatives to 2-methoxyphenyl, which may be more stable metabolically, led to the 2,3-dihydrobenzofuran **20** and the 2,3-dihydro-1,4-benzodioxin **21**. Disappointingly, both had inferior activity in AC.

Reversal of the 4-(aminomethyl)piperidyl bridging group gave racemate **22**, which had significantly reduced activity compared to compound **18**, consistent with the pyrimidine series.

At the time of this work, the only suggestions in the literature of how to obtain selectivity over α_1 activity in this class of compounds was through 7,8-benzofusion.[14] Therefore, substitution in these two positions was explored in order to determine whether selectivity over α_1 could be improved. As reported above, incorporation of an 8-methoxy substituent into the pyrimidine subseries actually increased affinity for α_1 receptors. A similar effect was seen in the 2-methoxyphenyl containing subseries, where introduction of an 8-fluoro substituent (compound **23**) led to good activity in vitro and in vivo. The relatively high α_1 affinity of this compound, however, precluded its further development, despite its low cataleptic activity. Introduction of a 7-chloro substituent (compound **24**) was found to give a more useful improvement, as affinity for rat α_1 receptors was not too high. Indeed, when human receptors were examined, selectivity for D_2, D_3, and 5-HT_{1A} receptors over α_1 receptors was much improved (see later). In addition, the duration of action of **24** in AC was now greater than 6 h, and the ED_{50} for catalepsy was increased to 188 mg/kg, 100-fold greater than its ED_{50} for antagonism of limbic amphetamine-induced locomotor activity, 1.8 mg/kg. The corresponding ratios for haloperidol, clozapine, olanzapine, and risperidone are 4, 9, 10, and 22, respectively (Figure 1). Because compound **24** had a desirable receptor binding profile and showed good in vivo activity, it was selected for further evaluation.

Against a panel of other neurotransmitter receptors, including 5-HT_{1A} and α_1 receptors from postmortem human brain (Table 2), **24** was found to have high affinity only for hD_{2L}, hD_3, and h5-HT_{1A} subtypes, with moderate affinity being shown for $hD_{4.2}$, 5-HT_7, and 5-HT_{2C}. The encouraging separation between affinities shown by **24** for human D_2-like and 5-HT_{1A} versus α_1 receptors suggests postural hypotension is unlikely to be significant in clinical studies with this compound.

Compound **24** increased levels of the dopamine metabolites DOPAC and HVA in the rat brain with ED_{20} of 2 mg/kg for DOPAC in both limbic and striatal tissue thereby demonstrating functional dopamine antagonism. Also in rat brain, **24** reduced levels of the 5-HT

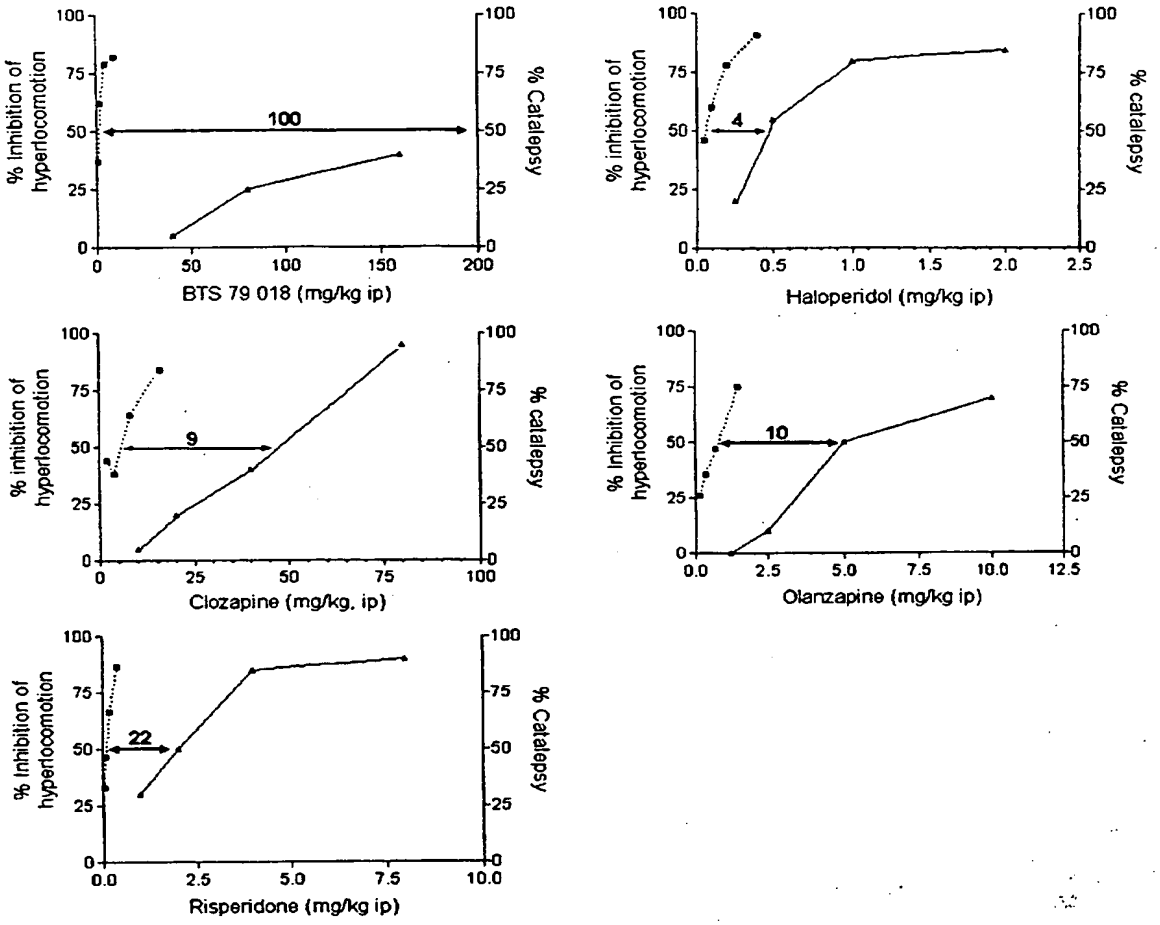


Figure 1. Comparison of the effects on catalepsy and amphetamine hyperlocomotion for BTS 79 018 (24) and reference compounds. Key: percent catalepsy (▲—▲), percent inhibition of amphetamine hyperlocomotion (■···■), therapeutic index (extrapolated for 24) (↔). Compound 24, like the comparator antipsychotics, potently inhibits amphetamine-induced hyperlocomotion in rats after ip administration; but unlike the other drugs, it shows a very low propensity to induce catalepsy. The ratio of the ED_{50} of a drug to attenuate amphetamine-induced hyperlocomotion (highly predictive of antipsychotic efficacy) to its ED_{50} to induce catalepsy (highly predictive of movement disorder liability) provides a therapeutic index for the drug. The ratios were calculated from the following ED_{50} values (mg/kg with 90% confidence limits). Compound 24: hyperlocomotion 1.8 (0.78–3.9); catalepsy 190 (79–450). Clozapine: hyperlocomotion 3.9 (1.7–8.8); catalepsy 34 (19–160). Haloperidol: hyperlocomotion 0.08 (0.03–0.22); catalepsy 0.44 (0.15–1.4). Olanzapine: hyperlocomotion 0.63 (0.28–1.4); catalepsy 6.1 (3.1–12). Risperidone: hyperlocomotion 0.078 (0.029–0.21); catalepsy 1.8 (0.82–3.8). Compound 24 clearly has the best therapeutic index of any drug tested; as expected haloperidol has the worst (24 ≫ risperidone > olanzapine > clozapine > haloperidol).

Table 2. Further Receptor Binding Affinities for 24 (BTS 79 018)[a]

hD_1 >1000	hD_{2L} 13.2 ± 3.4	hD_3 1.6 ± .09	$hD_{4.2}$ 70.9 ± 12.3	hD_5 >1000	h5-HT_{1A} 3.6 ± 0.5
$h\alpha_1$ 181 ± 18	α_{2D} >500	5-HT_{1B} >1000	5-HT_{2A} >500	5-HT_{2C} 58 ± 3.9	5-HT_3 >1000
5-HT_4 >1000	5-HT_6 >500	5-HT_7 27 ± 5	MCB >1000	H_1 >1000	

[a] K_i values (nM) ± SEM.

precursor 5-HTP by 25% at a dose of 30 mg/kg, consistent with an agonist effect at 5-HT_{1A} receptors. Compound **24** showed no effect in the Porsolt test at 100 mg/kg, but reversed the effect of 8-OH-DPAT in this test, with an ED_{50} of 11.9 mg/kg. Taken together these data demonstrate in vivo 5-HT_{1A} partial agonist activity.

Compound **24**, BTS 79 018, demonstrated the requisite activity in rodent models of antipsychotic activity, together with a predicted low propensity to cause extrapyramidal and cardiovascular side effects. It has, therefore, been selected for clinical studies to determine its potential as a novel atypical antipsychotic therapeutic agent.

Conclusion

Synthesis of analogues of the lead *N*-substituted (2,3-dihydro-1,4-benzodioxin-2-yl)methylamine derivative **1** resulted in the optimization of in vitro receptor binding activity and in vivo activity in rodent models of psychosis, leading to compound **24**, which had the required

good affinities for human D_2/D_3 and 5-HT_{1A} receptors, with significantly lower affinity for human α_1 adrenoceptors and rat H_1 and muscarinic receptors. In rodents, **24** showed functional D_2-like antagonism and 5-HT_{1A} partial agonism. After oral dosing most analogues showed good activity in rodent antipsychotic tests. This was combined in compound **24** with a long duration of action and very little potential to cause EPS, as measured by its ability to induce catalepsy in rats only at very high doses compared to doses effective in antipsychotic models. In light of this promising profile of activity, **24** has been selected for clinical investigation as a novel antipsychotic agent with a predicted low propensity to cause EPS.

Experimental Section

Chemistry. Proton magnetic resonance spectra were recorded on Bruker AM 360 or AC 250 spectrometers and are reported in ppm on the δ scale from internal tetramethylsilane. Infrared spectra were obtained using a Mattson-Unicam 3000 FTIR spectrometer. Elemental analyses were determined by the Physical Chemistry Department (Knoll Pharmaceuticals, Nottingham). Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Thin-layer chromatography was performed using Merck silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica 60 A. The term "dried" refers to use of anhydrous magnesium or sodium sulfate. A general description of the synthetic procedure is given where applicable.

Preparation of (2,3-Dihydro-1,4-benzodioxin-2-yl)methyl 4-Toluenesulfonates 25a–i, 48. General Procedure for the 4-Toluenesulfonylation of (2,3-Dihydro-1,4-benzodioxin-2-yl)methanols 27a–i, 47, e.g., (*R*)-(8-Fluoro-2,3-dihydro-1,4-benzodioxin-2-yl)methyl 4-Toluenesulfonate 25. A stirred solution of (*S*)-(8-fluoro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol **27g** (3.85 g, 20.9 mmol) in pyridine (50 mL) was treated with 4-toluenesulfonyl chloride (4.10 g, 21.6 mmol), and the resulting solution was stirred overnight at room temperature. The reaction mixture was poured into excess hydrochloric acid (5 M) and extracted with ethyl acetate. The combined extracts were washed with brine, dried, and concentrated under reduced pressure to give **25g** (4.10 g, 58%): ^{1}H NMR (DMSO-d_6) δ 7.77 (d, J = 8.3 Hz, 2H, 4-toluenesulfonyl *m*-H), 7.42 (d, J = 8.3 Hz, 2H, 4-toluenesulfonyl *o*-H), 6.75 (m, 2H, aromatic H), 6.58 (m, 1H, aromatic H), 4.48 (m, 1H), 4.25 (m, 3H), 4.04 (m, 1H), and 2.38 (s, 3H, Me).

Preparation of (2,3-Dihydro-1,4-benzodioxin-2-yl)methanols 27b–i, 47. 2,3-Dihydro-1,4-benzodioxin-2-ylmethanols **27b**,[20] **27c**,[20] **27d**,[21] **27e**,[22] and **47**[23] were synthesized according to literature procedures. Compound **27a** was purchased from a commercial supplier.

(*S*)-(7-Chloro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (27f). A stirred solution of 5-chlorosalicylaldehyde **30a** (8.92 g, 57.0 mmol) in dry dimethylformamide (200 mL) was treated with potassium carbonate (7.87 g, 57.0 mmol) and (*R*)-glycidyl 4-toluenesulfonylate (13.0 g, 57.0 mmol) and the mixture heated with stirring at 60 °C for 5 h. The mixture was then cooled and water (200 mL) added. The resulting mixture was extracted with ether (3 × 150 mL), and the combined extracts were washed with brine, dried, and concentrated under reduced pressure to give an oil. The residue was purified by flash column chromatography on silica eluting with a 25:1 mixture of petroleum ether (bp 40–60 °C) and ethyl acetate and then a 10:1 mixture of petroleum ether (bp 40–60 °C) and ethyl acetate to give (*R*)-5-chloro-2-(2,3-epoxypropoxy)benzaldehyde **31a** (8.10 g, 67%) as a colorless oil which solidified on standing: ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H, CHO), 7.80 (d, J = 2.7 Hz, 1H, aromatic H), 7.48 (dd, J = 8.9, 2.7 Hz, 1H, aromatic H), 6.97 (d, J = 8.9 Hz, 1H, aromatic H), 4.40 (dd, J = 11.1, 2.7 Hz, 1H), 4.06 (m, 1H), 3.41 (m, 1H), 2.96 (t, J = 4.6 Hz, 1H), and 2.78 (m, 1H).

3-Chloroperoxybenzoic acid (86%; 9.20 g, 45.87 mmol) was added to a stirred solution of **31a** (8.10 g, 38.11 mmol) in dichloromethane (100 mL), and the mixture was heated under reflux for 20 h and then cooled to room temperature. The resulting solid was filtered off and washed with dichloromethane. The filtrate was washed with saturated aqueous sodium metabisulfite solution (100 mL), saturated aqueous sodium bicarbonate solution (2 × 100 mL), and brine (100 mL), dried, and concentrated under reduced pressure to give (*R*)-5-chloro-2-(2,3-epoxypropoxy)phenyl formate **32a** (7.98 g, 92%) as an orange oil: IR (film) 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H, OCHO), 7.19 (dd, J = 8.8, 2.6 Hz, 1H, aromatic H), 7.12 (d, J = 2.6 Hz, 1H, aromatic H), 6.96 (d, J = 8.8 Hz, 1H, aromatic H), 4.26 (dd, J = 8.0, 2.9 Hz, 1H), 3.95 (m, 1H), 3.30 (m, 1H), 2.88 (t, J = 4.7 Hz, 1H), and 2.72 (m, 1H).

A solution of the epoxide **32a** (5.67 g, 24.81 mmol) in methanol (80 mL) was added slowly to a stirred solution of sodium methoxide, prepared from sodium (0.65 g, 28.26 mmol) and methanol (50 mL) under nitrogen. The resulting solution was stirred overnight at room temperature and concentrated under reduced pressure, and the residue was partitioned between ether and water. The ether layer was then washed with brine, dried, and concentrated under reduced pressure to give (*S*)-(7-chloro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol **27f** (4.40 g, 88%) as a pale-yellow solid, mp 61–62 °C: ^{1}H NMR ($CDCl_3$) δ 6.90 (d, J = 1.5 Hz, 1H, aromatic H), 6.80 (s, 2H, aromatic H), 4.24 (m, 2H), 4.11 (m, 1H), 3.86 (m, 2H), and 1.96 (t, J = 6.3 Hz, 1H, O*H*).

(*S*)-(8-Fluoro-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (27g). Alcohol **27g** was prepared following the same procedure as that for **27f** starting from 6-fluorosalicylaldehyde **30b**, which was synthesized by boron tribromide demethylation of 6-fluoro-2-methoxybenzaldehyde, which in turn was prepared by lithiation of 3-fluoroanisole and subsequent reaction with dimethylformamide following the procedure of Bridges et al.[28]

(*R,S*)-(5-Methoxy-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (27h) and (*R,S*)-(8-Methoxy-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (27i). Reaction of 3-methoxycatechol (60.2 g, 0.42 mol) with ethyl 2,3-dibromopropionate (90.0 g, 0.50 mol) and potassium carbonate (129.0 g, 0.94 mol) in acetone, using the literature conditions,[24] gave a mixture of 5-methoxy and 8-methoxy-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl esters **28a** and **28b** (83.8 g, 84%) which, by GC analysis, were in the approximate ratio of 2:1. A portion of the mixture (65.0 g, 0.27 mol) in absolute ethanol (160 mL) was treated with aqueous ammonia solution (SG 0.880; 500 mL) and the mixture stirred at room temperature for 90 min. The resulting white solid was collected by filtration, washed with a little water, and dried to give a mixture of the two carboxamides **29a** and **29b** (43.45 g, 77%). The mixture was then heated in boiling absolute ethanol (400 mL), and the insoluble material was collected by filtration and then once again heated in boiling absolute ethanol (25 mL). The resulting white solid was collected by filtration, washed with ethanol (20 mL), and dried to give **29a** (18.55 g, 33%) as a white solid, mp 196–198 °C; 97.3% pure by HPLC (S5 C8, MeCN/TEAF buffer 20:80, λ = 210 nm).

The filtrates from all of the ethanol digestions were combined and concentrated under reduced pressure. The residue was then purified by preparative HPLC (HP 1040M, sherisorb 5 μm C8, MeCN/TEAF buffer 20:80, λ = 205 nm) to give **29b** (8.10 g, 14%) as a white solid, mp 184–187 °C.

A stirred solution of the amide **29a** (18.40 g, 0.088 mol) in absolute ethanol (330 mL) was saturated with gaseous hydrogen chloride, and the mixture was heated under reflux for 16 h. The cooled reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was redissolved in ether, washed successively with water, 1 M aqueous sodium hydroxide solution, and water, dried, and concentrated under reduced pressure to give **28a** (18.55 g, 88%) as an oil, 97.5% pure by GC (3 ft, 10% OV-7).

A solution of the ester **28a** (18.54 g, 0.077 mol) in dry ether (100 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (2.0 g, 0.053 mol) in dry ether (150 mL) while the temperature of the reaction was maintained between 10 and 20 °C. The mixture was stirred at room temperature for 2 h and cooled to 5 °C, and then water (5 mL) was added cautiously. Aqueous sodium hydroxide solution (1 M; 12 mL) and water (12 mL) were then added, and the mixture was filtered through Celite. The filtrate was extracted with ether, and the combined extracts were washed with water, dried, and concentrated under reduced pressure to give (*R,S*)-(5-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl)methanol **27h** (12.50 g, 79%).

The above procedure was repeated for **29b** (8.0 g, 0.038 mol) giving **27i** (3.25 g, 36%), 95.69% pure by GC (OV-7).

General Procedure for the Preparation of the Amines 26a–g. 1-(1-Phenyl-4-piperidyl)methylamine (26a). A mixture of 1-chloro-2,4-dinitrobenzene (400 g, 1.98 mol) and isonicotinamide (200 g, 1.64 mol) was heated at 95 °C for 1 h. The resulting solid material was cooled, collected by filtration, and washed with a 10:1 solution of ether and methanol. The solid was then triturated with hot methanol (1000 mL), collected, and dried to give 4-carbamoyl-1-(2,4-dinitrophenyl)-pyridinium chloride **33** (449.1 g, 84%) as a cream solid, mp 233–36 °C: IR 1687 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.58 (d, J = 6.8 Hz, 2H), 9.13 (d, J = 2.5 Hz, 1H, aromatic H), 9.05 (br s, 1H, NH), 9.01 (dd, J = 8.7, 2.5 Hz, 1H, aromatic H), 8.75 (d, J = 6.8 Hz, 2H, aromatic H), and 8.44 (d, J = 8.7 Hz, 2H, aromatic H).

A mixture of **33** (50.0 g, 0.15 mol) and aniline (35.60 g, 0.38 mol) in methanol (1000 mL) was stirred at room temperature for 48 h. The resulting suspension was heated at 50 °C for 1 h, cooled, and concentrated under reduced pressure. The solid residue was triturated with acetone (2 × 1000 mL), filtered, and dried to give 4-carbamoyl-1-phenylpyridinium chloride **34a** (33.24 g, 92%) as an off-white solid, mp 290–292 °C: IR 1681 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.56 (d, J = 6.9 Hz, 2H, aromatic H), 9.12 (br s, 1H, NH), 8.67 (d, J = 6.9 Hz, 2H, aromatic H), 8.41 (br s, 1H, NH), 7.92 (m, 2H, aromatic H), and 7.76 (m, 3H, aromatic H). Anal. ($C_{12}H_{11}ClN_2O$) C, H, Cl, N.

A solution of the pyridinium salt **34a** (10.0 g, 42.64 mmol) in ethanol (250 mL) was hydrogenated at atmospheric pressure using hydrogen over a 10% palladium upon carbon catalyst (1.0 g). The catalyst was removed by filtration through Celite, and the filtrate was concentrated under reduced pressure to give 1-phenylpiperidine-4-carboxamide hydrochloride (**35a**) (8.79 g, 86%) as a solid: IR 1679 cm^{-1}.

The above amide hydrochloride **35a** (1.50 g, 6.24 mmol) was added portionwise to a stirred suspension of lithium aluminum hydride (0.50 g, 13.15 mmol) in dry tetrahydrofuran (100 mL), and the mixture was stirred at room temperature for 2 h and then at reflux for 2 h. The mixture was cooled, and water (0.5 mL) was carefully added. Concentrated aqueous sodium hydroxide solution (12.5 M; 0.5 mL) was then added, and the resulting precipitate was filtered through Celite. The filtrate was then dried and concentrated under reduced pressure to give 1-(1-phenyl-4-piperidyl)methylamine **26a** (1.15 g, 97%) as an oil: ^1H NMR ($CDCl_3$) δ 7.23 (m, 2H, aromatic H), 6.96 (d, J = 7.0 Hz, 2H, aromatic H), 6.82 (br t, J = 7.0 Hz, 1H, aromatic H), 3.70 (br d, J = 12.6 Hz, 2H), 2.63 (m, 4H), 1.81 (br d, J = 9.8 Hz, 2H), and 1.39 (m, 5H).

The remaining amines (**26b–g**) were synthesized in the same manner. 5-Amino-2,3-dihydro-1,4-benzodioxin (precursor to **26e**) was prepared according to the literature method,[29] and 7-amino-2,3-dihydrobenzo[*b*]furan (precursor to **26d**) was prepared by Raney nickel reduction of the corresponding known 7-nitro-2,3-dihydrobenzo[*b*]furan.[30]

Preparation of the Amines (26h–i). 4-(Aminomethyl)-1-(2-pyrimidinyl)piperidine (26i). Acetophenone (24.0 g, 0.2 mol) and 4-toluenesulfonic acid (0.40 g, 2.32 mmol) were added to a stirred solution of 4-(aminomethyl)piperidine (22.8 g, 0.2 mol) in dry toluene (200 mL), and the mixture was heated under reflux for 5 h under a Dean and Stark apparatus to give intermediate **36b**, which was not isolated. 2-Chloropyrimidine (22.9 g, 0.2 mol) and triethylamine (14 mL) were added to the resulting solution, and the mixture was heated at 95 °C with stirring for 18 h. The cooled reaction mixture was extracted with hydrochloric acid (5 M; 2 × 200 mL), and the combined extracts were heated at 95 °C for 6 h. The resulting cooled acidic solution was washed with ether and then basified with 5 M aqueous sodium hydroxide solution. The basic solution was extracted with ether, and the extracts were dried and concentrated under reduced pressure to leave a brown oil. The basic aqueous solution was also concentrated to dryness, and the resulting solid mass was extracted with ether. The combined extracts were dried and concentrated under reduced pressure to afford a brown oil. The combined brown oils were dissolved in ether and saturated with dry hydrogen chloride gas. The solid obtained was recrystallized from industrial methylated spirit to yield 4-(aminomethyl)-1-(2-pyrimidinyl)-piperidine 1.6 hydrochloride **26i** (16.50 g, 66%) as a yellow solid, mp 245–248 °C: ^1H NMR (DMSO-d_6) δ 8.43 (d, J = 4.9 Hz, 2H, pyrimidine 4,6-H), 8.24 (br s, 2H, NH_2), 6.72 (t, J = 4.9 Hz, 1H, pyrimidine 5-H), 4.66 (br d, J = 13.3 Hz, 2H), 2.98 (br t, J = 12.2 Hz, 2H), 2.69 (m, 2H), 1.92 (m, 1H), 1.83 (br d, J = 13.3 Hz, 2H), and 1.17 (dq, J = 12.2, 4.0 Hz, 2H). Anal. ($C_{10}H_{16}N_4 \cdot 1.6HCl$) C, H, N, Cl.

The amine **26h** was prepared in a similar manner by direct reaction of 4-(aminomethyl)piperidine with 2-chloropyridine and sodium carbonate in *iso*-amyl alcohol.

General Procedure for Alkylation of Amines 26a–i by the (2,3-Dihydro-1,4-benzodioxin-2-ylmethyl 4-Toluenesulfonates 25a–i, 48, e.g., Preparation of *N*-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-1-(1-phenylpiperid-4-yl)methylamine Dihydrochloride (14). A stirred mixture of the 4-toluenesulfonylate **25a** (10.10 g, 0.032 mol), the amine **26a** (6.0 g, 0.032 mol), and potassium carbonate (15.0 g, 0.11 mol) in acetonitrile (200 mL) was heated under reflux for 72 h and then cooled to room temperature. The resulting mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and purified by elution through a silica pad, using ethyl acetate as eluant, to give an oil after evaporation of solvent. The oil was dissolved in ether and saturated with hydrogen chloride. The resulting solid was collected by filtration and triturated with a 25:1 solution of ethyl acetate in methanol to give *N*-(2,3-dihydro-1,4-benzodioxin-2-yl)-1-(phenylpiperid-4-yl)methylamine dihydrochloride (**14**) (5.64 g, 43%), mp 278–280 °C: ^1H NMR (DMSO-d_6) δ 9.75 (br s, 1H, HCl), 9.55 (br s, 1H, HCl), 7.87 (br s, 2H aromatic H), 7.50 (m, 3H aromatic H), 6.89 (m, 4H aromatic H), 4.81 (m, 1H), 4.44 (dd, J = 11.7, 2.3 Hz, 1H), 4.08 (dd, J = 11.7, 6.6 Hz, 1H), 3.30 (m, 8H) and 2.09 (m, 5H). Anal. ($C_{21}H_{26}N_2O_2 \cdot 2HCl$) C, H, Cl, N.

Compounds **1–4**, **6–7**, **12–13**, **15–21**, **23–24**, and **49** were prepared by similar procedures.

For chiral compounds **1** and **18**, the (*R*)-4-toluenesulfonylate **25b**, prepared from the (*S*)-alcohol **27b**, was used in the reaction with the appropriate amine. Similarly, for **2** and **19** the (*S*)-4-toluenesulfonylate **25c**, prepared from the (*R*)-alcohol **27b**, was employed. The enantiomers **12** and **13** were separated by chiral HPLC (Chiralcel OC column eluting with hexane/ethanol 1:1 at 5 then 10 mL/min). Specific rotations and, where determined, HPLC derived enantiomeric excesses for all chiral target compounds are given below:

1 $[\alpha]_D$ −51.2° (c = 1.0, MeOH) 85.4% e.e. (Chiralcel OC hexane/ethanol 1:1); **2** $[\alpha]_D$ +49.5° (c = 1.0, MeOH) 84.8% e.e (Chiralcel OC, hexane/ethanol 1:1); **8** $[\alpha]_D$ −63.0° (c = 1.0 MeOH) 100% e.e.; **9** $[\alpha]_D$ +63.0° (c = 1.0, MeOH) 100% e.e. **12** $[\alpha]_D$ −63.0° (c = 1.0, MeOH) 100% e.e. (Chiralcel OC hexane/ethanol 1:1); **13** $[\alpha]_D$ +63.0° (c = 1.0, MeOH) 100% e.e (Chiralcel OC, hexane/ethanol 1:1); **18** $[\alpha]_D$ −27.0° (c = 1.0 CH_2Cl_2); **19** $[\alpha]_D$ +25.3° (c = 1.0, CH_2Cl_2); **23** $[\alpha]_D$ −49.2° (c = 1.0, MeOH); **24** $[\alpha]_D$ −42.6° (c = 0.5, EtOH) 99.8% e.e (Chiralcel OD, isohexane/2-propanol 1:1 containing 0.1% diethylamine).

***N*-(8-Hydroxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl) 1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine (5).** A solution of potassium hydroxide (1.0 g, 17.8 mmol) in a mixture of water (19.7 mL) and ethanol (19.7 mL) was added portion

wise to 2-({1-[1-(2-methoxyphenyl)piperid-4-yl]methylamino}-methyl)-2,3-dihydro-1,4-benzodioxin-8-yl 4-toluenesulfonate **49** (0.59 g, 0.93 mmol), and the mixture was heated under reflux with stirring for 2.5 h. The cooled mixture was neutralized with glacial acetic acid and extracted with ether (3 × 100 mL). The combined extracts were left to stand overnight, and the resulting white solid was collected by filtration and dried to give *N*-(8-hydroxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine **5** (0.20 g, 64%), mp 116–119 °C: IR 3552 cm $^{-1}$; ^{1}H NMR (DMSO-d_6) δ 9.00 (br s, 1H, OH), 6.88 (m, 4H, aromatic H), 6.58 (t, J = 8.1 Hz, 1H, aromatic H), 6.36 (dd, J = 8.0, 1.5 Hz, 1H, aromatic H), 6.31 (dd, J = 8.0, 1.5 Hz, 1H, aromatic H), 4.30 (dd, J = 11.2, 2.1 Hz, 1H), 4.15 (m, 1H), 3.91 (dd, J = 11.2, 7.6 Hz, 1H), 3.76 (s, 3H, OMe), 2.77 (m, 2H), 1.78 (br d, J = 12.1 Hz, 2H), 1.51 (m, 1H), and 1.31 (m, 2H)—remaining signals are obscured by water and DMSO peaks. Anal. ($C_{22}H_{28}N_2O_4 \cdot 3.5H_2O$) C, H, N.

***N*-(2-Pyrimidinyl)-3-[1-(2,3-dihydro-1,4-benzodioxin-2-yl]methylamino)propylamine (10).** A suspension of 2,3-dihydro-1,4-benzodioxin-2-carbonitrile[31] (15.0 g, 0.093 mol) in dry ether (50 mL) was added portionwise to a stirred suspension of lithium aluminum hydride (5.25 g, 0.14 mol) in dry ether (100 mL). The mixture was then stirred and heated under reflux for 1 h. The cooled mixture was carefully treated with water (7 mL), aqueous sodium hydroxide solution (2 M; 7 mL), and then water (30 mL). The resulting mixture was filtered, and the solid was washed with ethyl acetate and water. The filtrate was separated, and the aqueous phase was extracted with ethyl acetate. The extracts and the original organic phase were combined, dried, and concentrated under reduced pressure to give 1-(2,3-dihydro-1,4-benzodioxan-2-yl)-methylamine **40** (12.20 g, 80%) as an orange oil, 98% pure by GC (OV-7).

A mixture of the product **40** from the previous reaction (6.0 g, 0.036 mol), *N*-(3-bromopropyl)phthalimide (9.75 g, 0.036 mol), and potassium carbonate (9.94 g, 0.072 mol) in dry acetonitrile (100 mL) was heated under reflux with stirring for 24 h. The mixture was cooled and filtered, and the filtrate was concentrated under reduced pressure to give an orange gum. The gum was then stirred in hydrochloric acid (5 M; 100 mL) to give a brown solid which was recrystallized from methanol to give the phthalimide hydrochloride **41** (7.10 g, 56%) as a cream solid, mp 225–300 °C. Anal. ($C_{20}H_{21}ClN_2O_4$) H, N; C: calcd, 61.8; found, 61.2.

Hydrazine hydrate (0.46 mL, 9.30 mmol) was added to a stirred suspension of the phthalimide **41** (3.00 g, 7.7 mmol) in methanol (50 mL), and the mixture was heated under reflux for 1 h. Concentrated hydrochloric acid (4 drops) was then added, and the mixture was stirred at room temperature for 1 h. A colorless solid which separated was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was triturated with ether to give the propylamine dihydrochloride **42** (2.00 g, 88%) as a cream solid, mp 235–240 °C; 97.3% pure by HPLC (Asahipak ODP-50, MeCN/TEAF buffer 5:95, λ = 249 nm).

A stirred mixture of the propylamine **42** (1.61 g, 7.25 mmol), potassium carbonate (2.00 g, 14.5 mmol), 2-chloropyrimidine (0.87 g, 7.25 mmol), and sodium iodide (0.1 g) in dry acetonitrile (60 mL) was heated at reflux under nitrogen for 5 days. The cooled mixture was filtered, and the filtrate was concentrated under reduced pressure to give a viscous oil which was purified by flash chromatography on silica using a 10:1 solution of ethyl acetate and triethylamine as eluant to give two products, both as colorless oils. The dihydrochloride salts of these two products were prepared by dissolution in ether and then saturation with gaseous hydrogen chloride. This gave 3-[1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)amino]-*N*-(2-pyrimidinyl)propylamine dihydrochloride **10** (0.80 g, 37%), mp 50–55 °C: ^{1}H NMR (DMSO-d_6) δ 9.91 (br s, 1H, HCl), 9.56 (br s, 1H, HCl), 8.96 (br s, 1H, NH), 8.61 (d, J = 5.2 Hz, 2H, pyrimidine 4,6-H), 6.87 (m, 5H, 4 aromatic H and pyrimidine 5-H), 4.74 (m, 1H), 4.42 (dd, J = 11.7, 2.3 Hz, 1H), 4.08 (dd, J = 11.7, 6.8 Hz, 1H), 3.57 (t, J = 6.5 Hz, 2H), 3.35 (m, 1H), 3.10 (m, 4H), and 2.04 (m, 2H). Anal. ($C_{16}H_{20}N_4O_2 \cdot 2HCl \cdot 0.1EtOAc \cdot 0.7H_2O$) C, H, Cl, N. The second product obtained was *N*-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-*N*-(2-pyrimidinyl)-3-(2-pyrimidinylamino)propylamine dihydrochloride **43** (0.46 g, 17%), mp 50–55 °C: ^{1}H NMR (DMSO-d_6) δ 8.99 (br s, 1H, HCl), 8.61 (d, J = 5.3 Hz, 2H, pyrimidine 4,6-H), 8.43 (d, J = 5.3 Hz, 2H, pyrimidine 4,6-H), 6.95 (t, J = 5.3 Hz, 1H, pyrimidine 5-H), 6.82 (m, 4 H, aromatic H), 6.73 (t, J = 5.3 Hz, 1H, pyrimidine 5-H), 6.30 (br s, 1H, NH), 4.55 (m, 1H), 4.35 (dd, J = 11.6, 2.2 Hz, 1H), 4.04 (dd, J = 11.6, 6.8 Hz, 1H), 3.70 (m, 6 H), and 1.95 (quintet, J = 6.4 Hz, 2H). Anal ($C_{20}H_{22}N_6O_2 \cdot 2HCl$, 0.2EtOAc, $1.4H_2O$) C, H, Cl, N.

***(S)*-*N*-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-*N*-methyl-1-[1-(2-pyrimidinyl)-4-piperidyl]methylamine dihydrochloride (11).** A mixture of (*S*)-*N*-(2,3-dihydro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-pyrimidinyl)4-piperidyl]methylamine **1** (0.23 g, 0.56 mmol), sodium formate (0.13 g, 1.9 mmol), and formaldehyde (38–40% aqueous solution; 7 mL) was treated with formic acid (3 mL) while the temperature of the reaction was maintained between 5 and 10 °C. The mixture was then stirred at room temperature for 104 h, poured into water, and basified with 5 M aqueous sodium hydroxide solution. The cooled solution was then extracted with ether, washed with water, dried, and concentrated under reduced pressure to leave an oil (0.16 g). The oil was dissolved in ether and treated with hydrogen chloride gas giving (*S*)-*N*-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-*N*-methyl-1-[1-(2-pyrimidinyl)-4-piperidyl]methylamine dihydrochloride (**11**) (0.11 g, 46%) as a white solid, mp 235–240 °C: IR 3417 and 2800–2400 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 10.68 (br s, 1H), 8.41 (d, J = 4.8 Hz, 2H, pyrimidine 4,6-H), 6.90 (m, 4H, aromatic H), 6.68 (t, J = 4.8 Hz, 1H, pyrimidine 5-H), 4.95 (m,1H), 4.65 (br d, J = 13.0 Hz, 2H), 4.36 (d, J = 11.4 Hz, 1H), 2.80–3.60 (m, 10H), 2.19 (m, 1H), 1.92 (m, 2H), and 1.16 (m, 2H), some peaks obscured by broad water peak δ 4.1. Anal ($C_{20}H_{28}Cl_2N_4O_2 \cdot 1.2H_2O$) C, H, N.

(−)-1-[1-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)piperid-4-yl]-*N*-(pyrimidin-2-yl)methylamine (8) and (+)-1-[1-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)piperid-4-yl]-*N*-(pyrimidin-2-yl)methylamine (9). A solution of 4-(aminomethyl)piperidine (11.63 g, 0.1 mol) and 5-chlorosalicylaldehyde (16.0 g, 0.1 mol) in a 1:1 mixture of ethanol and methanol (400 mL) was stirred at room temperature for 4.5 h. The solution was then concentrated under reduced pressure to give *N*-(5-chloro-2-hydroxybenzylidene)-1-piperid-4-ylmethylamine (**45**) (25.7 g, 100%) as a yellow solid which was used without purification.

A mixture of **45** (25.5 g, 0.1 mol) and the 4-toluenesulfonylate **25a** (16.97 g, 0.053 mol) in dry dimethyl sulfoxide (200 mL) was heated with stirring at 100 °C for 3 h. The cooled mixture was poured into water (400 mL) and extracted with ethyl acetate. The combined extracts were dried and evaporated under reduced pressure to afford a brown oil which solidified on standing. Recrystallization from ethanol furnished 1-[1-(1,4-benzodioxan-2-ylmethyl)piperid-4-yl]-*N*-(5-chloro-2-hydroxybenzylidene)methylamine (**46**) (14.02 g, 66%) as a yellow solid, mp 94–96 °C: ^{1}H NMR (DMSO-d_6) δ 13.71 (br s, 1H, OH), 8.52 (br s, 1H, N=CH), 7.55 (d, J = 2 Hz, 1H aromatic H), 7.35 (dd, J = 8 Hz, 2 Hz, 1H, aromatic H), 6.8 (m, 5H, aromatic H), 4.30 (m, 2H) 3.93 (m, 1H), 3.50 (d, J = 5.5 Hz, 2H), 2.93 (m, 2H), 2.55 (m, 2H), 2.03 (br q, J = 12 Hz 2H), 1.61 (m, 3H), and 1.26 (m, 2H).

A solution of the product from the previous reaction (14.(g, 0.036 mol) in a 4:1 mixture of methanol and water (300 mL and hydrochloric acid (5 M; 45 mL) was stirred at room temperature for 1.5 h. The mixture was then concentrated under reduced pressure, and the resulting mixture was washed with diethyl ether. The aqueous solution was then basified with 5 M sodium hydroxide and extracted with ethyl acetate The combined extracts were dried and evaporated under reduced pressure to give 1-[1-(1,4-benzodioxan-2-ylmethyl) piperid-4-yl]methylamine (8.00 g, 87%) as a brown oil: G(96.6% (10% OV-7).

The amine product above (9.25 g, 0.035 mol) and 2-chlor pyrimidine (4.01 g, 0.035 mol) were added to a mixture c toluene (300 mL) and triethylamine (14 mL), and the resultin

solution was stirred and heated at 95 °C for 72 h. The cooled mixture was evaporated, and the residue was dissolved in water (100 mL). The solution was extracted with ethyl acetate, and the combined extracts were dried and evaporated to leave a brown oil. Trituration with diethyl ether afforded a brown solid (1.55 g), mp 88–94 °C. The aqueous phase was re-extracted with ethyl acetate, the combined extracts were dried and evaporated, and the resulting brown oil was triturated with isopropyl alcohol to give additional brown solid (0.93 g), mp 94–96 °C. On standing, a solid precipitated from the filtrate and was collected by filtration. The solid was washed with diethyl ether to give a tan colored solid (1.01 g). The three solids isolated above were combined and washed with diethyl ether to give racemic 1-[1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)piperid-4-yl]-*N*-(pyrimidin-2-yl)methylamine (1.23 g, 10%) as a tan solid. The enantiomers were then separated by preparative chiral HPLC (column Chiralcel OD, mobile phase 20% ethanol in cyclohexane) to give (−)-1-[1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)piperid-4-yl]-*N*-(pyrimidin-2-yl)methylamine (0.44 g) as a solid, mp 88–90 °C: $[\alpha]_D = -24.6°$ (c = 1.0, CH_2Cl_2); ^1H NMR (DMSO-d_6) δ 8.23 (d, J = 5 Hz, 2H, pyrimidine 4,6-H), 7.17 (t, J = 6 Hz, 1H, $HNCH_2$), 6.81 (m, 4H, aromatic H), 6.51 (t, J = 5 Hz, 1H, pyrimidine 5-H), 4.29 (m, 2H), 3.93 (m, 1H), 3.15 (t, J = 6 Hz, 2H), 2.91 (m, 2H), 2.54 (m, 2H), 1.95 (br q, J = 12 Hz, 2H), 1.61 (m, 3H), and 1.20 (m, 2H), and (+)-1-[1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)piperid-4-yl]-*N*-(pyrimidin-2-yl)methylamine (0.52 g) as a solid, mp 84–87 °C; which was less enantiomerically pure as shown by its optical rotation $[\alpha]_D = +16°$ (c = 1.0, CH_2Cl_2): ^1H NMR (DMSO-d_6) δ 8.23 (d, J = 5 Hz, 2H, pyrimidine 4,6-H), 7.17 (t, J = 5 Hz, 1H, $HNCH_2$), 6.82 (m, 4H, aromatic H), 6.51 (t, J = 5 Hz, 1H, pyrimidine 5-H), 4.29 (m, 2H), 3.93 (m, 1H), 3.15 (t, J = 6 Hz, 2H), 2.88 (m, 2H), 2.52 (m, 2H), 1.97 (br q, J = 12 Hz, 2H), 1.62 (m, 3H), and 1.18 (m, 2H).

1-[1-(2,3-Dihydro-1,4-benzodioxin-2-ylmethyl)-4-piperidyl]-*N*-(2-methoxyphenyl)methylamine Oxalate (22). A stirred mixture of 2-(chloromethyl)-2,3-dihydro-1,4-benzodioxin[32] (20.0 g, 0.108 mol) and ethyl piperidine-4-carboxylate (34.0 g, 0.217 mol) was heated at 130 °C for 3 h. The mixture was then cooled, diluted with ether, and filtered. The filtrate was concentrated under reduced pressure, and volatile byproducts were removed by vacuum distillation. The residual oil was then purified by flash column chromatography on silica using a 30:1 solution of dichloromethane and industrial methylated spirit as eluant to give ethyl 1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)piperidine-4-carboxylate **37** (23.3 g, 71%) as a brown oil. Anal. ($C_{17}H_{23}NO_4$) C, H, N.

A solution of the ester **37** (5.0 g, 0.164 mol) in industrial methylated spirit (100 mL) was added to a stirred solution of potassium hydroxide (4.0 g, 0.071 mol) in water (50 mL), and the mixture was stirred at room temperature for 1 h and then at reflux for 6 h. The cooled solution was concentrated under reduced pressure, and the residue was diluted with water and neutralized with hydrochloric acid (5 M). The aqueous mixture was then concentrated under reduced pressure, and the residue was triturated with a 25:1 solution of dichloromethane and methanol. The inorganic material was removed by filtration, and the filtrate was concentrated under reduced pressure to give crude 1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)piperidine-4-carboxylic acid **38** (5.03 g).

Ethyl chloroformate (0.90 g, 8.30 mmol) was added dropwise to a stirred solution of the carboxylic acid **38** (2.52 g, 8.97 mmol) and triethylamine (1.08 g, 10.70 mmol) in chloroform (90 mL) at 0 °C. After 30 min a solution of 2-methoxyaniline (1.08 g, 8.80 mmol) in chloroform (45 mL) was added, and the mixture was stirred at room temperature overnight and then at 50 °C for 1 h. The cooled mixture was then concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica using a 1:1 mixture of ethyl acetate and petroleum ether (bp 40–60 °C) as eluant to give 1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-*N*-(2-methoxyphenyl)piperidine-4-carboxamide **39** (1.05 g, 31%): ^1H NMR ($CDCl_3$) δ 8.39 (dd, J = 7.8, 1.7 Hz, 1H, aromatic H), 7.85 (br s, 1H, NH), 6.90 (m, 7H), 4.32 (m, 2H), 4.02 (m, 1H), 3.89 (s, 3H, OMe), 3.06 (m, 2H), 2.63 (m, 2H), 2.24 (m, 3H), and 1.90 (m, 4H).

A stirred solution of the amide **39** (1.69 g, 4.4 mmol) in dry tetrahydrofuran (100 mL) was treated with borane-dimethyl sulfide complex (1.0 M solution in tetrahydrofuran; 1.9 mL, 19 mmol), and the mixture was heated at reflux for 2 h. The mixture was cooled, and the solvent was removed under reduced pressure. Hydrochloric acid (2 M) was added to the residue, and the mixture was heated at 95 °C for 90 min. The mixture was cooled, basified with 5 M aqueous sodium hydroxide solution, and extracted with dichloromethane. The organic solution was washed with water, dried, and concentrated under reduced pressure. The residue was dissolved in ethyl acetate, and a warm solution of oxalic acid (0.20 g, 16 mmol) in ethyl acetate was added. The resulting precipitated solid was collected by filtration and dried to give 1-[1-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-4-piperidyl]-*N*-(2-methoxyphenyl)methylamine oxalate **22** (0.78 g, 38%), mp 215–218 °C: IR 3424 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.80 (m, 6H, aromatic H), 6.51 (m, 2H, aromatic H), 4.63 (m, 1H), 4.29 (dd, J = 11.5, 2.3 Hz, 1H), 4.00 (m, 1H), 3.77 (s, 3H, OMe), 3.35 (m, 2H), 3.10 (m, 2H), 2.99 (d, J = 6.1 Hz, 2H), 2.73 (m, 2H), 1.83 (m, 3H), and 1.41 (m, 2H). Anal. ($C_{22}H_{28}N_2O_3(COOH)_2 \cdot 0.1H_2O$) C, H, N.

Binding Assays. Assay methods and radioligands for the cloned human dopamine D_{1-5} receptors and animal derived D_2, 5-HT_{2A}, α_1, α_{2D}, muscarinic, and H_1 receptors were as previously described.[3] For percent displacement of radioligand at 10^{-6} M the specific binding in the absence and presence of test compound was determined. The percentage displacement of specific binding was then calculated manually. For K_i determinations, the IC_{50} values were calculated using the iterative curve-fitting program EBDA. K_i values were then calculated using the Cheng and Prusoff equation.

5-HT_{1A} Receptor Binding Assay in Rat Brain. 1. Membrane Preparation. Adult male CD rats were killed by cervical dislocation, their brains removed, and hippocampii (100–120 mg) immediately dissected. Tissue was homogenized in ice-cold 50 mM Tris-HCl, pH 7.7 (at 25 °C, 1:40 w/v), using a motor-driven Teflon pestle (12 strokes, 800 rpm) and centrifuged at 40000g for 10 min. To remove endogenous 5-HT, the pellet was rehomogenized in 50 mM Tris-HCl, pH 7.7 (1:40 w/v), incubated at 37 °C for 10 min, and then recentrifuged at 40000g for 10 min. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.7, containing 4 mM calcium chloride, 0.1% L-ascorbic acid, and 10 μM pargyline hydrochloride (equivalent to 6.25 mg wet weight of tissue/mL) and used immediately in the binding assay. All centrifugations were carried out at 4 °C.

2. Binding Assay. Membranes (400 μL; equivalent to 2.5 mg wet weight of tissue/tube) were incubated with 50 μL of [^{3}H]8-OH-DPAT at a single concentration of 2 nM and 50 μL of distilled water (total binding) or 50 μL of test compound (10^{-6} M) or 50 μL of 5-HT (10 μM; nonspecific binding) for 30 min at 25 °C.

Membrane-bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 50 mM Tris-HCl, pH 7.7 (wash setting 9,9,0), and radioactivity determined by liquid scintillation counting (1 mL Packard MV Gold scintillator).

5-HT_{1B} Receptor Binding Assay in Pig Brain. 1. Membrane Preparation. Pig caudate was homogenized in ice-cold 50 mM Tris-HCl, pH 7.7 (at 25 °C, 1:100 w/v), using a motor-driven Teflon pestle (8 strokes, 800 rpm) and centrifuged at 40000g for 10 min. The resulting pellet was resuspended in 50 mM Tris-HCl, pH 7.7 (1:100 w/v), incubated at 37 °C for 10 min to remove endogenous 5-HT, and then recentrifuged at 40000g for 10 min. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.7 (equivalent to 33.3 mg wet weight of tissue/mL), and used immediately in the binding assay. All centrifugations were carried out at 4 °C.

2. Binding Assay. Membranes (300 μL; equivalent to 10

mg wet weight of tissue/tube) were incubated with 50 μL of [^{3}H]sumatriptan at a single concentration of 4 nM; 50 μL of 50 mM Tris-HCl, pH 7.7; 50 μL of 50 mM Tris-HCl, pH 7.7, containing 50 mM calcium chloride, 100 μM pargyline hydrochloride, and 1% L-ascorbic acid; and 50 μL of distilled water (total binding), or 50 μL of drug solution (10^{-6} M), or 50 μL of 5-HT (10 μM; nonspecific binding) for 45 min at 25 °C. Membrane-bound radioactivity was recovered by filtration under vacuum through Whatman GF/B filters, previously soaked in 0.5% polyethylenimine using a Brandel cell harvester. Filters were rapidly washed with 16 mL of ice-cold 50 mM Tris-HCl, pH 7.7, and radioactivity was determined by liquid scintillation counting (2 mL Packard MV Gold scintillator).

5-HT$_{2C}$ Receptor Binding Assay in Pig Brain. 1. Membrane Preparation. Pig choroid plexus was homogenized in ice-cold 0.32 M sucrose (1:30 w/v) with a Kinematic polytron (speed setting 6 for 30 s) and centrifuged at 1000*g* for 10 min. The supernatant was stored on ice, and the pellet was rehomogenized in 0.32 M sucrose (1:15 w/v) and centrifuged at 850*g* for 12 min. Combined supernatants were diluted to 1:80 w/v with ice-cold 50 mM Tris-HCl, pH 7.4 (at 25 °C), and centrifuged at 40000*g* for 10 min. The resulting pellet was resuspended in 50 mM Tris-HCl, pH 7.4 (1:80 w/v), preincubated for 10 min at 37 °C to remove endogenous 5-HT, and centrifuged at 40000*g* for 10 min. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.4, containing 4 mM calcium chloride, 0.1% L-ascorbic acid, and 10 μM pargyline hydrochloride (equivalent to 12.5 mg wet weight of tissue/mL). All centrifugations were carried out at 4 °C.

2. Binding Assay. Membranes (800 μL; equivalent to 10 mg wet weight of tissue/tube) were incubated with 100 μL of [^{3}H]mesulergine at a single concentration of 1 nM and 100 μL of distilled water (total binding) or 100 μL of drug solution (10^{-6} M or at 10 concentrations ranging from 10^{-11}–10^{-4} M) or 100 μL of 5-HT (10 μM; nonspecific binding) for 30 min at 37 °C. Membrane-bound radioactivity was recovered by filtration under vacuum through Whatman GF/C filters presoaked for 1 h in 0.5% polyethylenimine, using a Brandel cell harvester. Filters were rapidly washed with 12 mL of ice-cold 50 mM Tris-HCl, pH 7.4, and radioactivity determined by liquid scintillation counting (2 mL Packard MV Gold scintillator).

5-HT$_3$ Receptor Binding Assay in Rat Brain. 1. Membrane Preparation. Rat entorhinal cortices were homogenized in ice-cold 50 mM HEPES (*N*-2-hydroxyethylpiperazine-*N*-2-ethanesulfonic acid) buffer (pH 7.4 at 4 °C; 1:10 w/v) using a Soniprep 150 (setting 5–6 for 8 s) and centrifuged at 49000*g* for 10 min. The resulting pellet was homogenized in 50 mM HEPES buffer (1:10 w/v) and recentrifuged at 49000*g* for 10 min. The final pellet was resuspended in 50 mM HEPES buffer, pH 7.4 (equivalent to 40 mg wet weight of tissue/mL), and used immediately in the binding assay. All centrifugations were carried out at 4 °C.

2. Binding Assay. Membranes (200 μL; equivalent to 8 mg wet weight of tissue/tube) were incubated with 200 μL of [^{3}H]-GR 65630 at a single concentration of 0.2 nM and 100 μL of 50 mM HEPES buffer (total binding) or 100 μL of drug solution (10^{-6} M) or 100 μL of metoclopramide (30 μM; nonspecific binding) for 30 min at 37 °C. Membrane-bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 50 mM HEPES buffer, pH 7.4 (wash setting 9,9,0), and radioactivity determined by liquid scintillation counting (1 mL Packard MV Gold scintillator).

5-HT$_4$ Receptor Binding Assay in Pig Brain. 1. Membrane Preparation. Pig hippocampii were homogenized in ice-cold 50 mM HEPES buffer (pH 7.4 at 4 °C; 1:15 w/v) using a Soniprep 150 (setting 5–6 for 8 s) and centrifuged at 40000*g* for 15 min. The resulting pellet was resuspended in 50 mM HEPES buffer, pH 7.4 (equivalent to 20 mg wet weight of tissue/mL), and used immediately in the binding assay. All centrifugations were carried out at 4 °C.

2. Binding Assay. Membranes (400 μL; equivalent to 8 mg wet weight of tissue/tube) were incubated with 50 μL of [^{3}H]-GR 113808 at a single concentration of 0.1 nM and 50 μL of 50 mM HEPES buffer (total binding) or 50 μL of drug solution (10^{-6} M) or 50 μL of 5-HT (30 μM; nonspecific binding) for 30 min at 37 °C. Membrane-bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters, presoaked for 1 h in 0.5% polyethylenimine, using a Skatron cell harvester. Filters were rapidly washed with ice-cold 50 mM HEPES buffer, pH 7.4 (wash setting 9,9,0), and radioactivity determined by liquid scintillation counting (1 mL Packard MV Gold scintillator).

Rat Recombinant 5-HT$_6$ Receptor Binding Assay. 1. Membrane Preparation. Frozen membranes from SF9 insect cells, infected with baculovirus to express the rat recombinant 5-HT$_6$ receptor, were used. Membrane fragments were thawed, resuspended in 50 mM Tris-HCl, pH 7.4 (at 25 °C), containing 10 mM magnesium sulfate and 0.5 mM ethylenediaminetetraacetic acid (EDTA) (equivalent to 35 μg of membrane protein/mL), and used immediately in the binding assay.

2. Binding Assay. Membranes (400 μL; equivalent to 14 μg of membrane protein/tube) were incubated with 50 μL of [^{3}H]lysergic acid diethylamide ([^{3}H]LSD) at a single concentration of 3 nM and 50 μL of distilled water (total binding) or 50 μL of drug solution (10^{-6} M) or 50 μL of methiothepin (10 μM; nonspecific binding) for 90 min at 27 °C. Membrane-bound radioactivity was recovered by filtration under vacuum through Whatman GF/C filters, presoaked for 1 h in 0.3% polyethylenimine, using a Skatron cell harvester. Filters were washed with ice-cold 50 mM Tris-HCl, pH 7.4 (wash setting 9,9,0), and radioactivity was determined by liquid scintillation counting (1 mL Packard MV Gold scintillator).

Rat Recombinant 5-HT$_7$ Receptor Binding Assay. 1. Membrane Preparation. Frozen membranes from SF9 insect cells, infected with baculovirus to express the rat recombinant 5-HT$_7$ receptor, were used. Membrane fragments were thawed, resuspended in 50 mM Tris-HCl, pH 7.4 (at 25 °C), containing 10 mM magnesium sulfate and 0.5 mM EDTA (equivalent to 5 μg of membrane protein/mL), and used immediately in the binding assay.

2. Binding Assay. Membranes (400 μL; equivalent to 2 μg of membrane protein/tube) were incubated with 50 μL of [^{3}H]-lysergic acid diethylamide ([^{3}H]LSD) at a single concentration of 3 nM and 50 μL of distilled water (total binding) or 50 μL of drug solution (10^{-6}M) or 50 μL of methiothepin (10 μM; nonspecific binding) for 90 min at 27 °C. Membrane-bound radioactivity was recovered by filtration under vacuum through Whatman GF/C filters, presoaked for 1 h in 0.3% polyethylenimine, using a Skatron cell harvester. Filters were washed with ice-cold 50 mM Tris-HCl, pH 7.4 (wash setting 9,9,0), and radioactivity determined by liquid scintillation counting (1 mL Packard MV Gold scintillator).

α_1 Adrenoceptor Binding in Postmortem Human Brain. 1. Membrane Preparation. Postmortem human cortex was homogenized in ice-cold 0.25 M sucrose (1:30 w/v) using a motor-driven Teflon pestle and centrifuged at 1000*g* for 10 min. The supernatant was stored on ice, and the pellet was resuspended in 0.25 M sucrose (1:15 w/v) and centrifuged at 750*g* for 10 min. Combined supernatants were diluted to 1:80 w/v with ice-cold 50 mM Tris-HCl, pH 7.4 (at 25 °C), and centrifuged at 28000*g* for 10 min. The resulting pellet was stored at −80 °C until the day of assay. The pellet was then resuspended in 50 mM Tris-HCl, pH 7.6 (1:40 w/v), and centrifuged at 40000*g* for 10 min. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.6 (equivalent to 12.5 mg wet weight of tissue/mL), and used immediately in the binding assay. All centrifugations were carried out at 4 °C.

2. Binding Assay. Membranes (400 μL; equivalent to 5 mg wet weight of tissue/tube) were incubated with 50 μL of [^{3}H]-prazosin at a single concentration of 0.1 nM and 50 μL of distilled water (total binding) or 50 μL of drug solution (10^{-6} M or a range of 10 concentrations) or 50 μL of phentolamine (5 μM; nonspecific binding) for 30 min at 30 °C. Membrane-bound radioactivity was recovered by filtration under vacuum

through Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 50 mM Tris-HCl, pH 7.6 (wash setting 9,9,0), and radioactivity determined by liquid scintillation counting (1 mL Packard MV Gold scintillator).

5-HT$_{1A}$ Receptor Binding in Postmortem Human Brain. 1. Membrane Preparation. Postmortem human hippocampi were homogenized in ice-cold 0.25 M sucrose (1:30 w/v) using a motor-driven Teflon pestle and centrifuged at 1000*g* for 10 min. The supernatant was stored on ice and the pellet was resuspended in 0.25 M sucrose (1:15 w/v) and centrifuged at 850*g* for 10 min. Combined supernatants were diluted to 1:80 w/v with ice-cold 50 mM Tris-HCl, pH 7.7 (at 25 °C), and centrifuged at 40000*g* for 10 min. The pellet was then resuspended in 50 mM Tris-HCl, pH 7.7 (1:40 w/v), and preincubated at 37 °C for 10 min to remove endogenous 5-HT. The membrane suspension was then centrifuged at 40000*g* for 10 min. The final pellet was resuspended in 50 mM Tris-HCl, pH 7.7, containing 4 mM calcium chloride, 0.1% L-ascorbic acid, and 10 μM pargyline hydrochloride (equivalent to 12.5 mg wet weight of tissue/mL) and used immediately in the binding assay. All centrifugations were carried out at 4 °C.

2. Binding Assay. Membranes (400 μL; equivalent to 5 mg wet weight of tissue/tube) were incubated with 50 μL of [^{3}H]8-OH-DPAT at a single concentration of 0.75 nM and 50 μL of distilled water (total binding) or 50 μL of drug solution (10^{-6} M or a range of 10 concentrations) or 50 μL of 5-HT (10 μM; nonspecific binding) for 30 min at 25 °C. Membrane-bound radioactivity was recovered by filtration under vacuum through Skatron 11734 filters using a Skatron cell harvester. Filters were rapidly washed with ice-cold 50 mM Tris-HCl, pH 7.7 (wash setting 9,9,0), and radioactivity determined by liquid scintillation counting (1 mL Packard MV Gold scintillator).

Biochemical Assays. Levels of the 5-HT precursor 5-HTP in rat brain were determined according to the method of Heal et al.[33] Levels of the dopamine metabolites DOPAC and HVA were determined by a modification of the method of Digory and Buckett.[34]

Behavioral Tests. 1. Antagonism of Apomorphine-Induced Climbing. Groups of 10 male CD1 mice (20–25 g; Charles River, U.K.) received appropriate concentrations of test compound or vehicle (0.1 mL/kg) po, at appropriate times prior to 0.88 mg/kg apomorphine sc. Immediately after the dose of apomorphine, mice were placed individually into inverted, open-ended wire cages and climbing behavior was assessed on a simple 0–2 ranking scale, at 10 and 20 min after apomorphine administration. ED_{50} values (doses causing 50% of control score) and 95% confidence limits were calculated by an adaption of the method of Litchfield and Wilcoxon.[35]

2. Antagonism of Amphetamine-Induced Hyperlocomotion. Male CD rats (150–240 g; Charles River, U.K.) were placed individually into plexiglass test cages and allowed to acclimatize fully prior to testing. Groups of 8 rats received test compound or vehicle (1 mL/kg) ip, at appropriate times prior to 2.5 mg/kg *d*-amphetamine sulfate, sc. Locomotor activity was assessed by infrared detectors for 15 min following the administration of amphetamine, and ED_{50} values (doses causing 50% of control activity counts) and 95% confidence limits were calculated by an adaption of the method of Litchfield and Wilcoxon.[35]

3. Catalepsy. Groups of five male rats (130–190 g; Charles River, U.K.) were injected ip with test compound solution (1 mL/kg) at appropriate concentrations. Catalepsy was assessed at three time points, by gently placing each rat paw on a 45 mm rubber bung, in turn. A score of 1 was given for every paw that remained on the bung for 15 s (maximum score for group: 20 = 100% catalepsy). ED_{50} values were determined from the percent catalepsy at the final reading. ED_{50} determination was by an adaption of the method of Litchfield and Wilcoxon.[35]

Determination of 5-HT$_{1A}$ receptor agonism by use of the Porsolt test, in the presence and absence of 8-OH-DPAT, was carried out using the method of Luscombe et al.[36]

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